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Clinical impact of women with gestational diabetes mellitus by the new consensus criteria: two year experience in a single institution in Japan

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Abstract. There is a paucity of information on perinatal data regarding gestational diabetes mellitus (GDM) by the new criteria from a real experience because the number of health care associations implementing the new criteria is still limited. The aim of this study is to investigate perinatal features of the new criteria-defined GDM. We reviewed a total of 995 women with singleton pregnancy that underwent GDM screening followed by a diagnostic oral glucose tolerance test (OGTT). All women found to have GDM underwent self-monitoring of blood glucose measurements as well as dietary management. Insulin treatment was initiated when dietary treatment did not achieve the glycemic goal. Of the 995 women, 141 had GDM (14.2%): 104 with one, 27 with two, and 10 with three abnormal OGTT values. Women with two or three abnormal OGTT values (2/3-AV) needed insulin treatment more frequently than those with one abnormal OGTT value (1-AV) (70.3% vs 23.1%, $P < 0.0001$). After adjustment for age, pregravid overweight, gestational weeks at diagnosis, a first-degree family history of diabetes was correlated with the implementation of insulin treatment in women with 1-AV (adjusted odds ratio 3.9; 95% Confidence Interval 1.7-9.2; $P = 0.001$). When compared perinatal outcomes between women with normal glucose tolerance and GDM, fetal growth and the occurrence of pregnancy-induced hypertension were comparable between the two groups. Our data suggest that the IADPSG-defined GDM with 1-AV show less severe glucose intolerance, but might be at risk of insulin requirement when a first-degree family history of diabetes exists.

Key words: The new consensus criteria, Gestational diabetes mellitus, Large-for gestational age, Gestational hypertension

IN 2010, International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed new criteria for diagnosing and classifying gestational diabetes mellitus (GDM), based on data of the observational hyperglycemia and adverse pregnancy outcomes (HAPO) study [1]. Since the new diagnostic criteria would increase the frequency of GDM diagnosis without a detailed cost-effectiveness analysis, the number of health care associations implementing the new criteria is still limited [2]. Thus, there is a paucity of information on the IADPSG-defined GDM from a real experi-

ence. Especially, clinical significance of GDM by one abnormal value under the IADPSG criteria remains unknown [3].

In Japan, the IADPSG recommendation was adopted in July 2010 [4], and is commonly used in the obstetric practice, although the screening strategy varies in hospitals. With this background, we have investigated perinatal outcomes of the IADPSG-defined GDM in our hospital. First, maternal clinical and metabolic features were compared between women with a single and two or three abnormal oral glucose tolerance test (1- and 2/3-AV) values. Second, factors associated with insulin treatment in women with 1-AV were investigated. Third, perinatal outcomes were compared between women with normal glucose tolerance and IADPSG-defined GDM.

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Materials and Methods

Subjects

We conducted a retrospective cohort study of 995 consecutive pregnant Japanese women who were cared for at the perinatal unit of Keio University Hospital from 2011 to 2012. Gestational age was confirmed in the first trimester by crown-rump length measurements. Excluded from this study were women with multi-fetal pregnancies and women whose neonates exhibited congenital anomalies. Women with a medical history indicating either impaired glucose tolerance or diabetes mellitus (DM), or the use of medications known to affect glucose metabolism were also excluded. The research was performed in accordance with the Declaration of Helsinki and informed consent was obtained from patients where appropriate. This study was approved by the institutional review board at Keio University School of Medicine.

GDM screening and glycemic control

Each woman underwent a two-step screening for GDM: universal early testing and a standard 1-h 50g oral glucose challenge test (GCT) in early and late pregnancy, respectively, based on the clinical recommendation by Japan Society of Obstetrics and Gynecology (JSOG) [4]. The universal early testing included the clinical risk factors, as follows: (1) pregravid overweight (BMI ≥ 25), (2) prior GDM, (3) past history of macrosomia (birth weight ≥ 4000 g), (4) a family history of DM in the first-degree relatives, (5) random plasma glucose ≥ 95 mg/dL. Levels of HbA1c and glycoalbumin (GA) were also examined as early testing in our institution (cut-off values: HbA1c $\geq 5.9\%$, GA $\geq 15.8\%$). Women with positive early testing underwent a diagnostic 75-g OGTT with the measurement of plasma glucose (mg/dL) and insulin concentration (mU/L) in the fasting state and at 30 min, 1 h, and 2 h after the glucose load. Plasma glucose and insulin levels were measured by a glucose oxidase method and enzyme immunoassay, respectively. Women with negative early testing or normal OGTT results underwent a standard GCT between 24 and 27 weeks of gestation. If the GCT result exceeded 140 mg/dL, the diagnostic 75-g OGTT was then performed. Based on the IADPSG criteria, GDM was diagnosed if one or more values reached or exceeded the following thresholds: fasting, 92 mg/dL; 1 h, 180 mg/dL; 2 h, 153 mg/dL [1]. Overt diabetes in pregnancy was defined as HbA1c $\geq$

6.5% or fasting plasma glucose ≥ 126 mg/dL or random plasma glucose exceeded 200 mg/dL, the latter needing to be confirmed by one of the former [1]. The normal glucose tolerance (NGT) group comprised women with normal GCT or normal OGTT results.

All women found to have IADPSG-defined GDM underwent self-monitoring of blood glucose (SMBG) measurements as well as dietary management (daily calorie intake: early, 30 kcal/kg + 150 kcal; late, 30 kcal/kg + 350 kcal; if obese, 30 kcal/kg throughout pregnancy). Dietary management includes three meals and three snacks. Daily capillary glucose profiles were obtained seven times a day under dietary management: fasting, 2 h-post-breakfast, before lunch, 2 h-post-lunch, before dinner, 2 h-post-dinner, and bedtime. Capillary glucose levels were measured with a Medisafe Fit Pro blood glucose meter (Terumo Corporation, Tokyo, Japan). Insulin treatment was initiated when dietary treatment did not consistently maintain fasting and pre-meal capillary glucose ≤ 100 mg/dL and 2 h postprandial capillary glucose ≤ 120 mg/dL, respectively. Regular, or rapid acting, and NPH insulin were used to achieve the glycemic target and insulin dose was adjusted according to insulin algorithm based on SMBG values.

Assessment of insulin sensitivity, insulin secretion and beta cell function

Insulin sensitivity and insulin secretion were evaluated using measurements from the diagnostic OGTT [5, 6]. The insulin sensitivity was estimated by the whole-body insulin sensitivity index derived from the OGTT (IS_{OGTT}). The IS_{OGTT} was calculated by the following formula: $10,000 / \text{square root} \{ \text{Glu}_0 \times \text{Ins}_0 \times (\text{Glu}_0 + \text{Glu}_{60} \times 2 + \text{Glu}_{120}) / 2 \times (\text{Ins}_0 + \text{Ins}_{60} \times 2 + \text{Ins}_{120}) / 2 \}$, where Glu_y and Ins_y represent plasma glucose (mg/dL) and insulin values (mU/L), respectively, at time y min during the OGTT. Insulin secretion was assessed by the ratio of the total area under the insulin curve to the total area under the glucose curve (AUC_{ins/glu}) during the OGTT. To evaluate beta cell function, we calculated the OGTT-derived disposition index using the following measures: Insulin Secretion-Sensitivity Index-2 (ISSI-2: the AUC_{ins/glu} multiplied by IS_{OGTT}) [7].

Perinatal outcomes

Maternal characteristics and perinatal outcomes were collected from the patients' hospital records. Gestational hypertension was defined as a blood pres-

sure of at least 140/90 mmHg occurring for the first time after mid-pregnancy, without proteinuria or pre-existing hypertension. Proteinuria was defined as urinary excretion of at least 0.3 g in a 24-hour period. A diagnosis of preeclampsia was made in women who developed gestational hypertension and proteinuria. Using the Japanese standard sex- and parity-specific birthweight percentile curves, birthweight $\geq$ 90th percentile was defined as large-for-gestational age (LGA), and birthweight $<$ 10th percentile was designated small-for-gestational age (SGA). Macrosomia was defined as birthweight above 4000 g.

Statistical analysis

Data were presented as mean $\pm$ SD or percentage in text and tables, where appropriate. Continuous data were compared between groups by Student's *t* test. Categorical variables were analyzed with the chi-square test or Fisher's exact test. Statistical analysis was performed using the JMP (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was considered statistically significant.

Results

Among 995 pregnant women, 141 (14.2%) were diagnosed to have GDM: 104 with a single abnormal value, 27 with two abnormal values, and 10 with three abnormal values. Of women with GDM, 68 were diagnosed by universal early testing in the first trimester. Two women (2/995 cases, 0.2%) had overt diabetes in

pregnancy.

When compared the clinical features between women with 1- and 2/3-AV, there were no significant differences in maternal age, pregravid overweight (BMI $\geq$ 25), prior GDM, a family history of DM, and gestational weeks at diagnosis (Table 1). Compared with 1-AV, women with 2/3-AV showed significantly lower levels of IS_{OGTT} ($P < 0.01$), although insulin secretion assessed by AUC_{ins/glu} was comparable between the two groups. As a result, levels of ISSI-2 in women with 2/3-AV were significantly lower than those with 1-AV ($P < 0.0001$). To achieve glycemic goal, women with 2/3-AV needed insulin treatment more frequently than those with 1-AV (70.3% vs 23.1%, $P < 0.0001$, Table 1).

With respect to clinical features in the 1-AV group, there were no significant differences in metabolic phenotypes (insulin sensitivity, insulin secretion, and beta cell function) as well as maternal age, pregravid overweight (BMI $\geq$ 25), prior GDM, gestational weeks at diagnosis between women with and without insulin treatment (Table 2). Of interest, a family history of DM was more prevalent in women requiring insulin treatment (41.7% vs. 15.0%, $P < 0.01$, Table 2). The time point showing abnormal values as well as levels of plasma glucose and insulin at the diagnostic OGTT were not associated with the implementation of insulin treatment (Table 3). After adjustment for age, pregravid overweight, gestational weeks at diagnosis, a family history of DM was significantly correlated with insulin treatment in women with 1-AV (adjusted odds ratio 3.9; 95% Confidence Interval 1.7-9.2; $P = 0.001$).

Table 1 Maternal clinical features in women with a single and two/three abnormal oral glucose tolerance test results

		A single abnormal OGTT result (n=104)	Two/three abnormal OGTT results (n=37)
Maternal age	, years	35.7 $\pm$ 4.4	35.8 $\pm$ 4.8
Pregravid BMI	, kg/m ²	20.7 $\pm$ 3.4	22.3 $\pm$ 5.1*
Pregravid overweight		10 (9.6%)	8 (21.6%)
Prior GDM		1 (1.0%)	2 (5.4%)
A family history of diabetes		22 (21.2%)	11 (29.7%)
Gestational age at diagnosis	, weeks	21 $\pm$ 8	22 $\pm$ 7
Diagnosed before 20 weeks' pregnancy		51 (49.0%)	17 (46.0%)
HbA1c at diagnosis	, %	5.4 $\pm$ 0.3	5.4 $\pm$ 0.3
IS _{OGTT}		6.4 $\pm$ 3.0	4.8 $\pm$ 2.7 [#]
AUC _{ins/glu}		0.34 $\pm$ 0.21	0.41 $\pm$ 0.22
ISSI-2		2.1 $\pm$ 0.62	1.6 $\pm$ 0.49 ^{##}
Insulin treatment		24 (23.1%)	26 (70.3%) ^{###}

OGTT, oral glucose tolerance test; BMI, body mass index; overweight, BMI $\geq$ 25; GDM, gestational diabetes mellitus; IS_{OGTT}, insulin sensitivity index derived from the oral glucose tolerance test; AUC_{ins/glu}, the ratio of the total area under the insulin curve to the total area under the glucose curve during the oral glucose tolerance test; ISSI-2, Insulin Secretion-Sensitivity Index-2 (*i.e.* the AUC_{ins/glu} multiplied by IS_{OGTT}); *, $P < 0.05$; [#], $P < 0.01$; ^{##}, $P < 0.0001$

Table 2 Maternal characteristics in women with a single abnormal oral glucose tolerance test result

		Insulin treatment (n=24)	Dietary management only (n=80)
Maternal age	, years	36.1 ± 5.0	35.9 ± 4.3
Pregravid BMI	, kg/m ²	21.1 ± 2.6	20.5 ± 3.6
Pregravid overweight		3 (12.5%)	7 (8.8%)
Prior GDM		0 (0.0%)	1 (1.25%)
A family history of diabetes		10 (41.7%)	12 (15.0%) [#]
Gestational age at diagnosis	, weeks	20 ± 8	22 ± 8
Diagnosed before 20 weeks' pregnancy		13 (54.2%)	38 (47.5%)
HbA1c at diagnosis	, %	5.4 ± 0.3	5.4 ± 0.3
IS _{OGTT}		6.6 ± 3.4	6.3 ± 2.9
AUC _{ins/glu}		0.37 ± 0.18	0.40 ± 0.22
ISSI-2		2.1 ± 0.74	2.1 ± 0.58

OGTT, oral glucose tolerance test; BMI, body mass index; overweight, BMI ≥ 25; GDM, gestational diabetes mellitus; IS_{OGTT}, insulin sensitivity index derived from the oral glucose tolerance test; AUC_{ins/glu}, the ratio of the total area under the insulin curve to the total area under the glucose curve during the oral glucose tolerance test; ISSI-2, Insulin Secretion-Sensitivity Index-2 (*i.e.* the AUC_{ins/glu} multiplied by IS_{OGTT}); [#], *P* < 0.01

Table 3 Profiles of the diagnostic oral glucose tolerance test in women with a single abnormal result

		Insulin treatment (n=24)	Dietary management only (n=80)
Plasma glucose (mg/dL)	0 min	89.3 ± 7.1	88.9 ± 7.4
	30 min	145.2 ± 17.8	141.7 ± 22.4
	60 min	152.8 ± 29.0	153.7 ± 27.3
	120 min	146.6 ± 29.6	135.8 ± 26.2
Plasma insulin (mU/L)	0 min	6.4 ± 3.2	6.6 ± 4.3
	30 min	58.9 ± 30.6	60.5 ± 38.9
	60 min	62.0 ± 34.7	71.4 ± 47.3
	120 min	69.2 ± 37.9	64.3 ± 41.5
Abnormal value of plasma glucose [#]	0 min	9 (37.5%)	40 (50%)
	60 min	3 (12.5%)	14 (17.5%)
	120 min	12 (50%)	26 (32.5%)

[#], Cases showing abnormal plasma glucose values at each time point in the diagnostic oral glucose tolerance test

The overall perinatal features of this study cohort were as follows: the mean maternal age was 34.9 ± 4.8 years, pregravid BMI 19.8 ± 4.6, gestational age at delivery 38.0 ± 2.4 weeks, mean birthweight 2841 ± 551 g, and 680 (68.0%) were primiparas. Twenty-five women (2.5%) developed gestational hypertension, and 19 (1.9%) preeclampsia. The occurrence of SGA and LGA was 6.9% (69/995 cases) and 6.0% (60/995 cases), respectively.

The baseline characteristics and pregnancy outcomes of women with NGT or GDM are shown in Table 4. There were significant differences in maternal age, pregravid overweight, and a family history of DM among subjects with NGT and GDM. With

regard to fetal growth, the prevalence of LGA and SGA were comparable between the NGT and GDM groups. Additionally, no significant differences in the occurrence of pregnancy-induced hypertension (*i.e.* gestational hypertension and preeclampsia) were found between the two groups.

Discussion

Currently, prospective data on the potential frequency of GDM with the IADPSG criteria has been slow. To the best of our knowledge, this is the first report on perinatal features of women with GDM in the clinical situations that adopted the IADPSG consen-

Table 4 Baseline characteristics and perinatal outcomes in women with normal glucose tolerance or gestational diabetes mellitus

		NGT (n=852)	GDM (n=141)
Maternal age	, years	34.7 ± 4.8	36.1 ± 4.6 *
Nulliparous		591 (69.4%)	89 (63.1%)
Pregravid BMI	, kg/m ²	19.6 ± 4.7	21.1 ± 4.0 #
Pregravid overweight		36 (4.2%)	18 (12.8%) ##
Prior GDM		5 (0.6%)	3 (2.1%)
A family history of diabetes		57 (6.7%)	33 (23.4%) ##
Gestational age at delivery	, weeks	38.1 ± 2.4	37.8 ± 2.8
Birth weight	, g	2845 ± 548	2821 ± 573
LGA		59 (6.9%)	10 (7.1%)
Macrosomia		9 (1.1%)	1 (0.7%)
SGA		53 (6.2%)	7 (5.0%)
Gestational hypertension		21 (2.5%)	4 (2.8%)
Preeclampsia		17 (2.0%)	2 (1.4%)

NGT, normal glucose tolerance, defined as negative screen for gestational diabetes mellitus or normal oral glucose tolerance results. GDM, gestational diabetes mellitus; BMI, body mass index, overweight, BMI ≥ 25; LGA, large-for-gestational age, defined as birth weight ≥ 90th percentile for gestational age; SGA, small-for-gestational age, defined as birth weight < 10th percentile for gestational age; Macrosomia, birth weight ≥ 4000g. *, $P < 0.05$; #, $P < 0.001$; ##, $P < 0.0001$.

sus criteria. In our institution, the prevalence of GDM by the former JSOG criteria was 2.3%, as previously reported [8]. Compared with the former situations, the IADPSG criteria lead to an increase in the frequency of GDM diagnosis in our hospital. Additionally, the majority (104/141 cases, 74%) of women with GDM showed 1-AV, which was consistent with data in the complete HAPO cohort [1]. Our results demonstrated that the frequency of GDM would increase significantly with the IADPSG criteria, mainly by those with 1-AV.

The implementation of insulin treatment was based on daily glucose profile during dietary management in our hospital. In this retrospective analysis, more women with 2/3-AV needed the addition of insulin treatment to achieve the glycemic control, compared with 1-AV. With respect to beta cell function, levels of ISSI-2 in women with 2/3-AV were significantly lower than those with 1-AV. The level of beta cell function is associated with the severity of glucose intolerance in GDM [9]. Additionally, our previous investigation demonstrated that beta cell dysfunction in women with 2/3-AV appeared more severe than those with 1-AV [10]. Taken altogether, our data indicated women with 2/3-AV had more severe levels of glucose intolerance, compared with 1-AV.

Approximately one-quarter of women with 1-AV needed the insulin treatment. Most women with the IADPSG-defined GDM have 1-AV and factors asso-

ciated with insulin treatment are needed in the clinical practice. The insulin treatment did not depend on which glucose result met or exceeded single IADPSG-defined OGTT threshold. When analyzed maternal characteristics, a family history of DM was correlated with the induction of insulin treatment. Of women with the IADPSG-defined GDM, therefore, those with 1-AV appear less severe glucose intolerant, but might be at risk of insulin requirement when a family history of DM exists.

There were significant differences in pregravid overweight, prior GDM, and a family history of DM among subjects with NGT and GDM, as were noted in the former situations [11]. Of note, no significant differences were found in the occurrence of perinatal outcome including LGA and pregnancy-induced hypertension between the NGT and GDM groups in this study cohort. Previous analysis based on reevaluated data before the adoption of the IADPSG criteria has shown increased risk of the development of LGA and gestational hypertension in the IADPSG-defined GDM [12]. Additionally, Black *et al.* have shown that IADPSG-defined GDM could be at risk of adverse outcomes including LGA, gestational hypertension and shoulder dystocia/birth injury [13]. To date, two trials have demonstrated the advantages of treatment for women with mild degree glucose intolerance, although inclusion criteria for the trial were different from the IADPSG rec-

ommendation [14-16]. Our results suggest that intervention for women with IADPSG-defined GDM could contribute to the improvement of pregnancy outcomes, although further studies on the clinical and cost-effective management are needed.

Benefit of treatment of IADPSG-defined GDM remains unknown because no randomized control trial has been conducted using the IADPSG criteria and additional well-designed trial and other clinical studies will be needed to determine the optimal treatment targets [1]. In the clinical settings, therefore, appropriate management of IADPSG-defined GDM remains unclear. Our data is only a local experience but could

be useful for other healthcare professionals considering the IADPSG criteria.

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Disclosure

Authors declare no conflict of interest with regard to this manuscript.

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