Title

Effect of the New Diagnostic Criteria for Gestational Diabetes Mellitus among Japanese Women

Abstract

Background : The new diagnostic criteria of gestational diabetes mellitus (GDM), which was proposed by the International Association of Diabetes and Pregnancy Study Groups in 2010, was recently accepted by Japan. Therefore, the frequency of GDM is four times higher than previously recorded. This means that GDM has become a more clinically important disease. This study aimed to assess how the number of patients with GDM and its complications have changed after adoption of the new criteria.

Methods: A total of 3,610 pregnant women in the Japan Assessment of GDM Screening Trial and Okayama University Hospital were included. We analyzed the prevalence of GDM and its complications using the old and new criteria.

Results: The prevalence of perinatal outcomes was increased by adopting the new criteria. There were many important perinatal complications in the additional new GDM criteria, and therefore patients with mild GDM, like one point disorder patients, should have careful intervention. Admission to the neonatal intensive care unit was significantly increased ($p=0.01$) according to the new GDM criteria because the old criteria are stricter than the new criteria. GDM patients with obesity (BMI $\geq$25 kg/m^2) had a high frequency of perinatal complications that may require active intervention and strict follow-up.

Conclusions : Because the new criteria of GDM greatly affect perinatal complications, intervention of GDM from an early stage and strict follow-up (especially GDM with obesity) are important for reducing complications, and diabetes and metabolic syndrome of the mother and child.

Key words New GDM criteria, perinatal complications, obesity, 75-g oral glucose tolerance test

Introduction

Diabetes mellitus (DM) has been increasing worldwide, especially in developed countries because of people's diet [1]. DM in Japan is also increasing every year. In 2007 approximately 22,100,000 patients in Japan had DM or a propensity to develop DM. DM and gestational DM (GDM) are common diseases during pregnancy. Gestational age is also related to glucose intolerance [2]. DM and GDM during pregnancy may result in many maternal and neonatal complications, such as macrosomia, fetal malformations, neonatal hypoglycemia, hyperbilirubinemia, and hypertension. Therefore, DM and GDM are important diseases that need to be managed during pregnancy. And, the number of patients with DM needs to be reduced. Identifying GDM is a good method of determining the potential for DM because mild glucose intolerance during pregnancy is easily observed. The current definition of GDM, as any DM found during pregnancy, was adopted 26 years ago. This definition needs to be changed to fit the current conditions. Criteria should be divided between GDM and DM. Therefore we changed the definition of the

GDM criteria as the onset of any glucose intolerance during pregnancy, except for overt diabetes in pregnancy based on an international consensus.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) published new universal diagnostic criteria based on the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study in 2010 [3,4]. In July 2010, the Japan Society of Obstetrics and Gynecology (JSOG) accepted the new diagnostic criteria of gestational diabetes mellitus (GDM), which were proposed by the IADPSG. JSOG changed the cutoff of the glucose value in each hour in the 75-g oral glucose tolerance test (OGTT) and began to diagnose GDM by using an abnormal glucose value at only one time point (instead of two time points) with the new diagnostic criteria. Moreover, we adopted the concept of overt diabetes in pregnancy. We found that the frequency of GDM rapidly increased because of the new criteria and GDM became an important clinical disease.

Materials and Methods

The current study included patients from the Japan Assessment of GDM Screening (JAGS) Trial (there were 3527 patients, including healthy patients in 28 hospitals from 2001 to 2011) and 83 GDM patients from Okayama University hospital between 2004 and 2010, with a total of 3610 patients. In the JAGS trial, all patients had a 75-g OGTT. We compared perinatal outcomes of the old and new GDM criteria by a retrospective case-control study.

Glucose values were measured three times (fasting, 1 h after, and 2 h after) in the 75-g OGTT. The old GDM criteria defined abnormal glucose values at two and three time points in the 75-g OGTT. The cutoff of glucose values for fasting was ≥100 mg/dl, 1 h after fasting was ≥180 mg/dl and 2 h after fasting was ≥150 mg/dl. All time points of glucose intolerance during pregnancy were included in the old criteria. The new GDM criteria were changed and defined abnormal glucose values at only one time point in the 75-g OGTT. The cutoff of glucose values for fasting was ≥92 mg/dl, 1 h after fasting was ≥180 mg/dl, and 2 h after fasting ≥153 mg/dl. Moreover, the concept of overt diabetes in pregnancy was adopted.

There were 2022 patients who had a 75-g OGTT in the first trimester. A total of 2832 patients had a 75-g OGTT in the second trimester (24-28 weeks of gestation), and these patients had at least one time point with an abnormal glucose value. However, whether the patients had treatment is unknown. Adverse perinatal outcomes were respiratory problems, macrosomia, fetal malformations, hyperbilirubinemia, neonatal hypoglycemia, preeclampsia, shoulder dystocia, and primary cesarean section. Additionally, we surveyed adverse perinatal outcomes of an additional 341 GDM patients because of the new GDM criteria. The additional GDM define the patients are in the new GDM criteria but they are not in the old GDM criteria.

Microsoft Excel 2010 for Windows 7 was used for statistical analysis. Statistical significance for perinatal

outcomes was determined using the Mann-Whitney U test. Statistical significance of complications between the new GDM and the old GDM, and between body mass index (BMI) ≥25 kg/m^2 and BMI <25 kg/m^2, was determined by the χ^2 test. Values of $p<0.05$ were considered significant.

Results

The maternal and perinatal characteristics of the 3610 women who agreed to participate in this study are shown in Table 1. BMI of the women diagnosed by old GDM criteria was significantly larger than that of the women diagnosed by new GDM criteria ($p=0.03$). There was no significant difference in the mean gestational age in weeks, 75-g OGTT results ,birth weight, delivery week, and the rate of preterm deliveries between both criteria.

The prevalence of GDM increased from 83/2839 patients (2.92%) to (363/2839patients) 12.08% by adopting the new criteria in the data of the JAGS trial. Unique complications of GDM were also increased according to the new criteria of GDM (Table 2). Admission to the neonatal intensive care unit (NICU) occurred in more (22/135; 16.3%) patients according to the old criteria for GDM compared with that in patients according to the new criteria for GDM (44/491; 9.0%, $p<0.05$). However, in patients with other complications (i.e., respiratory problems of newborns, macrosomia, fetal malformations, hyperbilirubinemia, neonatal hypoglycemia, shoulder dystocia, and pregnancy induced hypertension [PIH]), the number of complications appeared to be increased according to the new criteria, but there were no statistical difference between the two groups. The rate of primary cesarean delivery also increased from 19 to 48 patients, which meant that there was an increase by 2.5 times. 4 patients were IUFD in the first trimester (3for the additional GDM).1 patient was induced abortion in the second trimester to the old criteria for GDM. There is not neonatal death.

We also analyzed the difference in perinatal complications according to the new GDM criteria, which were diagnosed by one, two, and three time points that had abnormal glucose values in the 75-g OGTT. There were no differences in perinatal complications between patients who had one time point with an abnormal glucose value and those who had two time points with an abnormal glucose value for GDM. Patients who had one time point with an abnormal glucose value in the 75-g OGTT had as many complications as those who had two or three time points with an abnormal glucose value (Table 3).

The additional new GDM patients also had many perinatal complications, which were sometimes severe (Table 4). For example, there were four cases of macrosomia in patients who had one time point with an abnormal glucose value in the second trimester, although we could not find this complication according to the old GDM criteria. Six patients (three patients had one time point with an abnormal glucose value in the first trimester and the other three patients had one time point with an abnormal glucose value in the second trimester) had neonatal hypoglycemia, including one patient with hyperbilirubinemia and the birth weight was greater than 3500 g. Fetal malformations appeared in six patients. Three of these patients had one time point with an abnormal glucose value in the first trimester and the other three patients had one

time point with an abnormal glucose value in the second trimester. Two patients had cardiovascular disease, two patients had urinary disease, and the other two patients were unknown. Moreover, 23 of the additional new GDM patients (first trimester: nine patients; second trimester: 11 patients; both trimesters: three patients) had PIH. Seven patients had early onset PIH and 16 patients had late onset PIH. Two of these patients were operated on with emergency cesarean section because of severe superimposed preeclampsia. Ten of these patients had obesity (BMI ≥25 kg/m^2). These results suggest that PIH, GDM, and obesity may be related to each other.

There was a high incidence of GDM in PIH patients who had a BMI ≥25 kg/m^2; therefore, we investigated the occurrence of perinatal complications (Table 5). A total of 82 patients (16.7%) had GDM according to the new GDM criteria (n=491) and had a BMI of greater than 25 kg/m^2. A total of 409 of 491 (83.3%) patients did not have obesity. The proportions of patients with perinatal complications who had a BMI greater than 25 kg/m^2 and less than 25 kg/m^2 were 15.8% and 7.6% for admission to the NICU, 7.3% and 1.5% for fetal malformations, 1.2% and 0% for hypertrophic cardiomyopathy, and 14.9% and 5.9% for PIH, respectively. Therefore, patients who had a BMI greater than 25 kg/m^2 had a significantly higher incidence of complications than those with a BMI less than 25 kg/ m^2 ($p<0.05$).

Discussion

In our study, the frequency of GDM has increased from 2.92% according to the old criteria to 12.08% according to the new criteria. Therefore, there were 4.1 times as many patients according to the new GDM by adopting new diagnostic criteria for GDM in the JAGS trial. However, this frequency is based on the case where all patients had a 75-g OGTT. For those patients who had positive signs in screening (for example, a 50-g glucose challenge test), if they had had a 75-g OGTT instead, this frequency would be approximately 11% [5].

The number of patients with a given complication increased overall when the new GDM criteria were adopted. Admission to the NICU was only significant according to the new GDM criteria, because the old criteria were severe. However, there are many perinatal complications in mild GDM, suggesting that identifying mild GDM and intervention are useful for patients. Several randomized control trials (RCTs) [6, 7] have reported similar results. For example, macrosomia, which is unique to glucose intolerance according to the old GDM criteria, was not found in any patients, and according to the new GDM criteria, it was found in five patients. Therefore, clinical management might be inadequate for these five patients according to the new GDM criteria. We consider that treatment for these patients may reduce shoulder dystocia, cephalopelvic disproportion and emergency cesarean section, which are complications of macrosomia. A RCT reported that macrosomia is reduced by treatment for GDM [8]. Another retrospective case-control study reported that patients with diabetes have a higher risk of macrosomia than patients without diabetes [9]. Intervention is important because there are also many perinatal complications in the additional new GDM criteria. Blood glucose during pregnancy is also important for

perinatal outcome [10]. Therefore, we can expect to reduce several perinatal complications by monitoring blood glucose and active treatment of GDM. There are adverse complications of GDM through the first or the second trimester. We found that macrosomia, fetal malformations, neonatal hypoglycemia, and preeclampsia were present in screening of both the first and second trimesters for the additional new GDM criteria. Consequently, GDM should be screened for in the first and second trimesters. Screening for GDM is usually performed at the second trimester. Otherwise, some studies indicated the first trimester is also important for screening [11, 12].

In addition, GDM with obesity, which is also related to PIH, leads to frequent perinatal complications. Nilofer et al demonstrated that obesity is a significant risk factor in GDM. Additionally, adverse perinatal outcomes are increased by GDM [13]. In particular, GDM, PIH, and obesity may be closely related and strongly affect maternal quality of life, and children delivered from mothers with glucose intolerance may have metabolic syndrome (e.g., DM and hypertension) later in life [14]. Therefore, we should carefully manage patients with GDM and PIH, especially those with obesity, and intervene in each patient. In addition, the frequency of GDM is different between ethnicities. Asian women show a high percentage of GDM, but GDM with obesity is less common in Asians than in other races[15]. Maternal weight gain is also important for obstetric and neonatal outcomes [16-18]. In particular, weight gain with GDM is a high risk factor for perinatal complications [19]. Children whose mother has GDM may become obese [20]. Therefore, we have to carefully treat GDM patients regarding diet and weight gain during pregnancy.

Finally, identifying mild glucose intolerance due to physiological load during pregnancy could be useful for determining the potential for DM. Many studies have reported that GDM is associated with subsequent risks, such as type 2 diabetes mellitus or cardiometabolic risks [21-23]. Moreover, in offspring, metabolic syndrome may occur [24]. Patients with GDM according to the new GDM criteria have maternal and neonatal complications similar to those according to the old GDM criteria. Therefore, intervention in GDM and strict follow-up are important to reduce diabetic complications in pregnancy, and to reduce diabetes and metabolic syndrome in the mother and child later in life. Moreover, determining mild glucose intolerance according to the new GDM criteria is medically economical.

Conflict of Interest Statement All author declare that we have no conflict of interest.

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Table 1 : Maternal and perinatal characteristics

		All	Old GDM	New GDM
Gestational age (years-old)		30.26±7.03 （16-53）	32.41±4.41 （22-41）	31.9±4.78 （16-43）
BMI(kg/m^2)		21.1±14.6 （14-46.1）	23.5±6.76 （16.8-48.1）	22.3±5.93 （15-48.1）*
75gOGTT Gestational Weeks(weeks)	1st	9.99±2.64	10.20±3.55	10.09±2.81
	2nd	24.83±2.53	25.02±3.69	24.71 ±3.10
Birth weight (g)		3004±434	3037±488	3067±450
Gestational age at delivery(wk)		38.73±1.86	38.24±1.87	38.45±1.89
Rate of preterm delivery (%)		6.69	12.12	7.84

* : P<005(old GDM VS New GDM)

Table 2 : Prevalence of perinatal and neonatal outcomes according to the old and the new GDM criteria

	All	Old GDM	%	New GDM	%	P
All	3610	135	100	491	100	—
Admission to NICU	246	22	16.3	44	9.0	<0.05
PIH	226	12	8.9	36	7.3	N.S.
Macrosomia	30	0	0	5	1.0	N.S.
Infant weight ≧3500 g	316	17	12.6	52	10.6	N.S.
shoulder dystocia	5	1	0.7	2	0.4	N.S.
Respiratory problems	106	4	3.0	16	3.3	N.S.
neonatal hypoglycemia≦40mg/dl	57	5	3.7	14	2.9	N.S.
Hyperbilirubinemia T.Bil≧20mg/dl	25	2	1.5	3	0.6	N.S.
Polycythemia Ht≧65%	76	5	3.7	18	3.7	N.S.
Fetal malformations	63	5	3.7	12	2.4	N.S.
Hypocalcemia	13	0	0	1	0.2	N.S.
Hypertrophic cardiomyopathy	2	1	0.7	1	0.2	N.S.
Primary cesarean section	348	19	14.1	48	9.8	N.S.
Selective cesarean section	152	6	4.4	17	3.5	N.S.
Emergency cesarean section	196	13	9.6	31	6.3	N.S.
Body mass index≧25	304	34	25.2	73	14.9	N.S.

Table 3 : Frequency of perinatal and neonatal complications in the first and second trimesters and according to time points of abnormal glucose values in the 75-g OGTT with the new GDM criteria

	All	New GDM	1st Trimester OGTT	1st Trimester OGTT	2nd Trimester OGTT	2nd Trimester OGTT
			1Point	≧2Points	1Point	≧2Points
All	3610	491	180	63	179	69
Admission to NICU	246	44	16	8	8	16
PIH	226	36	12	5	17	6
Macrosomia	30	4	0	0	4	0
Shoulder dystocia	5	2	0	0	1	1
Respiratory problems	106	16	8	1	7	3
Neonatal hypoglycemia	57	14	4	7	5	2
Hyperbilirubinemia	19	3	2	1	1	1
Polycythemia	52	18	6	5	11	1
Fetal malformations	63	12	2	4	5	2
Hypocalcemia	13	1	1	0	0	0
Hypertrophic cardiomyopathy	2	1	0	1	0	1
Primary cesarean section	348	48	18	10	20	10

Table 4 : Frequencies of perinatal and neonatal complications in additional new GDM patients compared with those in all new GDM patients

	Additional new GDM	%	New GDM	%
All	341	100	491	100
Admission to NICU	20	5.8	44	9.1
PIH	23	6.7	36	7.3
Fetal malformation	4	1.2	4	0.8
Infant weight ≧3500g	40	11.7	52	10.6
shoulder dystocia	0	0	2	0.4
Respiratory problems	12	3.5	15	3.1
neonatal hypoglycemia	6	1.8	14	2.9
Hyperbilirubinemia	1	0.2	3	0.6
Polycythemia	12	3.5	18	3.7
Fetal malformations	6	1.8	12	2.4
Hypocalcemia	1	0.3	1	0.2
Body mass index≧25	42	12.3	73	14.9
Hypertrophic cardiomyopathy	0	0	1	0.2
Primary cesarean section	33	9.7	48	9.8
Selective cesarean section	13	3.8	17	3.5
Emergency cesarean section	20	5.9	31	6.3

Table 5 : Comparison of the frequency of perinatal complications according to BMI in women with the new GDM criteria

		BMI＜25		BMI≧25		
	New GDM	N	%	N	%	P
New GDM all	491	409	100	82	100	—
Admission to NICU	44	31	7.6	13	15.8	＜0.05
Macrosomia	4	3	0.7	1	1.2	N.S.
Infant weight ≧3500g	52	39	9.5	13	15.9	N.S.
Shoulder dystocia	2	1	0.2	1	1.2	N.S.
Respiratory problems	16	12	2.9	4	4.9	N.S.
Neonatal hypoglycemia	9	7	1.7	2	2.4	N.S.
Polycythemia	12	8	2.0	4	4.9	N.S.
Fetal malformations	12	6	1.5	6	7.3	＜0.05
Hypertrophic cardiomyopathy	1	0	0	1	1.2	＜0.05
Hypocalcemia	1	1	0.2	0	0	N.S.
Hyperbilirubinemia	5	4	1.0	1	1.2	N.S.
Preeclampsia	36	24	5.9	12	14.6	＜0.05
Emergency cesarean section	31	24	5.9	7	8.5	N.S.
Selective cesarean section	17	16	3.9	1	1.2	N.S.