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Original

Glycated Albumin May Predict Early Postpartum Glucose Intolerance in Patients with Gestational Diabetes

Keiko Yanagisawa,[1,2] **Mitsue Muraoka,**[3] **Koichiro Takagi,**[3] **Misa Kambara,**[1] **Sayoko Tanaka,**[1] **Tomoko Suzuki,**[1] **Hiroshi Sakura,**[2] and **Tetsuya Babazono**[1]

[1]Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan
[2]Department of Medicine, Tokyo Women's Medical University Medical Center East, Tokyo, Japan
[3]Department of Obstetrics and Gynecology, Tokyo Women's Medical University Medical Center East, Tokyo, Japan

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Gestational diabetes mellitus (GDM) is associated with an increased long-term risk of developing diabetes. We investigated the risk factors for early postpartum glucose intolerance in patients with GDM.
A total of 148 patients with GDM were included in this study. Among them, 30 and 118 were diagnosed with GDM before (B20w group) and after (A20w group) 20 weeks of gestation, respectively. Oral glucose tolerance test (OGTT) was performed in all patients 58 days after delivery. In each group, the association between the postpartum OGTT results and the following parameters were analyzed: age, BMI, family history of diabetes, plasma glucose levels in diagnostic prenatal OGTT, number of abnormal OGTT values, glycated hemoglobin and glycated albumin (GA) levels at diagnosis of GDM, serum C-peptide levels, frequency of insulin therapy, and pregnancy outcomes.
Postpartum OGTT revealed glucose intolerance in 9 and 35 patients in the B20w and A20w groups, respectively. In the B20w group, placental weight was an independent predictor for glucose intolerance. In the A20w group, GA level and family history were independent predictors for glucose intolerance.
Elevated GA levels may be associated with a higher risk of postpartum glucose intolerance in patients with GDM diagnosed after 20 weeks of gestation.

Key Words: gestational diabetes, postpartum, insulin therapy, glycated albumin

Introduction

Gestational diabetes mellitus (GDM) increases the risk of adverse pregnancy outcomes such as perinatal mortality, macrosomia, shoulder dystocia, preeclampsia, cesarean section, and neonatal complications. In addition, GDM is an associated with increased long-term risk of diabetes in mothers. A meta-analysis showed that women with a history of GDM had a seven-fold higher risk of developing type 2 diabetes than those who had normal glucose tolerance during pregnancy.[1] A systematic literature review reported a markedly increased risk for developing type 2

Corresponding Author: Keiko Yanagisawa, Diabetes Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. keikoy.dmc@twmu.ac.jp
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diabetes within the first five years after a pregnancy with GDM.[2] Therefore, the diagnosis of GDM offers the opportunity for identifying women at a high risk of developing glucose intolerance in the future. Some guidelines recommend a follow-up of women after a pregnancy with GDM.[3, 4] In the Guidelines for obstetrical practice in Japan, 2020 edition, women with GDM are recommended to undergo a 75-g oral glucose tolerance test (OGTT) 6-12 weeks after delivery.[3] The American Diabetes Association recommends that women with GDM should undergo OGTT at 4-12 weeks postpartum with repeat tests every 1-3 years if the postpartum OGTT is normal.[4] However, the number of women with a history of GDM who were followed up in the postpartum period was reported to be inadequately low.[5-10] Hence, a large number of women with a history of GDM developing type 2 diabetes may be neglected without testing.

In Japan, the number of women with GDM increased by at least 2.7-fold after adopting the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Criteria.[11] It has been reported that Asian women with GDM were associated with a higher risk of impaired glucose tolerance during the early postpartum period.[12, 13] Therefore, identifying women who have impaired glucose tolerance during the early postpartum period is important to facilitate follow-up management of women with GDM. The aim of this study was to assess potential predictors of early postpartum glucose intolerance in Japanese women with GDM diagnosed according to the IADPSG criteria.

Subjects and Methods

1. Subjects

We investigated a total of 154 women who were diagnosed with GDM using the IADPSG criteria and underwent an OGTT between 1-5 months after delivery at the Tokyo Women's Medical University Medical Center East, from April 2012 to February 2016. Among them, 148 women who had a singleton pregnancy were included in this study. Their median age was 35 (31, 38) years, and their median pre-gestational body mass index (BMI) was 21.7 (19.9, 24.7) kg/m^2. In our hospital, the two-step screening test for GDM was performed for each woman, and it was recommended for all of them to undergo a diagnostic OGTT when the random plasma glucose level was more than 100 mg/dL in early pregnancy or the plasma glucose level after a 50-g glucose challenge test exceeded 140 mg/dL in mid-pregnancy. Our hospital is a local core hospital where more than 30% of the women with GDM were referred from other hospitals. The subjects were divided into two groups according to the time of diagnosis of GDM: those diagnosed before (B20w group) and those diagnosed after (A20w group) 20 weeks of gestation.

2. Study methods

Glycated hemoglobin (HbA1c) and glycated albumin (GA) levels were measured at the time of GDM diagnosis or at the first visit to our hospital if the subject was referred to our hospital after the diagnosis, and the levels of C-peptide, triglycerides, high density lipoprotein (HDL)-cholesterol, and low density lipoprotein (LDL)-cholesterol were measured in fasting blood samples at the second visit, usually at 2 weeks after the first visit. After the women received dietary counselling (30 kcal/kg ideal body weight + 200 kcal) from a registered dietitian, if they had elevated fasting plasma glucose levels (> 100 mg/dL) or their 2h-postprandial glucose levels exceeded 120 mg/dL despite nutritional therapy and exercise, treatment with insulin commenced. An OGTT was performed on all subjects 58.0 ± 13.3 days after delivery. The subjects in the B20w and A20w groups were further divided into the following two subgroups: normal group, women with normal glucose tolerance; GI group, women with glucose intolerance including diabetes, impaired glucose tolerance or impaired fasting glucose according to the World Health Organization criteria.[14]

We evaluated the association between the results of postpartum OGTT and the following parameters: maternal age, height, pre-gestational body weight, pre-gestational BMI, family history of diabetes, number of parity, smoking status, number of abnormal values at diagnostic prenatal OGTT, gestational age at diagnosis of GDM, levels of plasma glucose in diagnostic prenatal OGTT, fasting serum C-peptide, triglycerides, HDL-cholesterol, LDL-cholesterol, HbA1c and GA, blood pressure and the pregnancy outcomes including weight gain during pregnancy, frequency of insulin therapy dur-

ing pregnancy, the gestational age at delivery, cesarean section, hypertensive disorders of pregnancy (HDP), birth weight and sex of neonate, placental weight, and neonatal complications such as respiratory problems, hypoglycemia, hyperbilirubinemia, congenital malformation, and neonatal intensive care unit (NICU) admission. Among neonatal complications, respiratory problems included respiratory distress syndrome, transient tachypnea of the newborn, apnea, and other respiratory disorders requiring clinical management. Neonatal hypoglycemia was defined as a blood glucose level in the neonate below 50 mg/dL. Neonates with hyperbilirubinemia underwent phototherapy. Congenital malformations were defined as structural or functional anomalies that impede life or those that cause dysfunction requiring surgical intervention. BMI was calculated using the following formula: body weight (kg) divided by the squared height (m^2).

Plasma glucose was determined by the hexokinase UV method (Labospect 7700, Hitachi, Tokyo, Japan) using Serotec GLU-HL (Serotec Co., Ltd., Sapporo, Japan). HbA1c level was analyzed by high-performance liquid chromatography assay (automated glycohemoglobin analyzer HLC ®-723G9; Tosoh Corp., Tokyo, Japan). GA was measured by an enzymatic method using a Lucica GA-L kit (Asahi Kasei Pharma,Tokyo, Japan). Serum C-peptide was determined by chemiluminescent enzyme immunoassay (Lumipulse Presto II; Fujirebio, Inc., Tokyo, Japan) using the Lumipulse Presto C-peptide reagent. Triglycerides, HDL-cholesterol, and LDL-cholesterol levels were measured using colorimetric analysis (LABSPECT 008, Hitachi Ltd.).

This study was conducted in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all subjects. This study was approved by the Ethical Committee of Tokyo Women's Medical University (Approval No. 4110R2, approval date: June 2, 2017).

3. Statistical analysis

All data were reported as mean ± standard deviation, median and inter-quartile range or a percentage of frequencies. We used the Student's t-test or Mann-Whitney U test and chi-square test to examine differences in continuous and categorical variables between the two groups, respectively. Subsequently, variables which were significantly related to postpartum glucose intolerance were included in the logistic regression analyses using enter method. All analyses were conducted using SPSS Statistics version 21 for Windows (IBM Corp., Armonk, NY, USA). A p-value of < 0.05 was considered to indicate statistical significance.

Results

1. Maternal characteristics in the B20w and A20w groups

Thirty women were diagnosed with GDM before 20 weeks of gestation (B20w group) and 118 women were diagnosed with GDM after 20 weeks of gestation (A20w group). The B20w group had higher pre-pregnancy BMI, fasting plasma glucose levels at diagnostic prenatal OGTT, and lower triglyceride levels than the A20w group (**Table 1**). Maternal age, frequencies of nulliparous women and family history of diabetes, levels of HbA1c and GA at diagnosis of GDM, and fasting serum C-peptide levels were similar between the two groups. Regarding pregnancy outcomes, the B20w group had higher frequency of insulin therapy during pregnancy and lower gestational weight gain than the A20w group. There were no differences between the two groups in terms of gestational age at delivery, frequency of cesarean section, birth weight of neonate, and frequency of neonatal complications.

2. Association of postpartum glucose tolerance status and clinical factors in the B20w group

In the B20w group, postpartum OGTT revealed glucose intolerance in 9 (30%) women (GI subgroup) [impaired glucose tolerance (IGT), 7; impaired fasting glucose (IFG)/IGT, 2] (**Table 2**).

Women in the GI subgroup had higher fasting glucose levels on OGTT at diagnosis of GDM than those in the normal subgroup. The number of abnormal values of diagnostic prenatal OGTT and, 1h- and 2h-glucose levels tended to be higher in the GI subgroup without any significant difference. There were no significant differences

Table 1 Clinical characteristics of women in the B20w and A20w groups.

	B20w group (n = 30)	A20w group (n = 118)	p
Maternal characteristics			
Age (years)	36 (34, 39)	35 (31, 38)	0.290
Height (cm)	157.9 ± 5.2	158.8 ± 5.1	0.414
Pre-pregnancy body weight (kg)	62 (52, 83)	54 (49, 61)	0.008
Pre-pregnancy BMI (kg/m^2)	23.9 (20.7, 32.0)	21.4 (19.7, 23.7)	0.004
Nulliparous, n (%)	13 (43)	72 (61)	0.099
Family history of DM, n (%)	12 (40)	60 (51)	0.313
Smoking, n (%)	7 (23)	26 (22)	1.000
GDM diagnosis			
Gestational age at diagnosis (weeks)	15.0 (13.1, 16.6)	27.8 (22.9, 30.0)	<0.001
OGTT plasma glucose (mg/dL)			
fasting	90 (81, 93)	83 (78, 92)	0.011
1h	186 (149, 213)	180 (159, 192)	0.058
2h	155 (144, 166)	157 (141, 169)	0.513
Number of abnormal values			
1 point, n (%)	13 (43)	75 (64)	0.113
2 points, n (%)	12 (40)	33 (28)	
3 points, n (%)	5 (17)	10 (8)	
HbA1c (%)	5.4 ± 0.4	5.3 ± 0.4	0.065
GA (%)	13.2 ± 1.4	13.1 ± 1.1	0.856
Fasting serum C-peptide (mg/dL)	1.41 (0.97, 1.72)	1.45 (1.13, 1.93)	0.389
Systolic blood pressure (mmHg)	112 ± 14	109 ± 11	0.378
Diastolic blood pressure (mmHg)	63 (57, 69)	61 (56, 65)	0.351
Serum lipid profiles			
Triglycerides (mg/dL)	170 (115, 228)	211 (169, 282)	0.005
HDL-cholesterol (mg/dL)	79 ± 17	83 ± 17	0.319
LDL-cholesterol (mg/dL)	135 (116, 158)	141 (120, 166)	0.457
Pregnancy outcome			
Insulin therapy during pregnancy, n (%)	16 (53)	33 (28)	0.016
HDP, n (%)	2 (7)	8 (7)	1.000
Gestational weight gain (kg)	5.3 ± 6.0	8.4 ± 4.1	0.012
Gestational age at delivery (weeks)	38.7 (38.0, 39.3)	39.0 (38.3, 39.4)	0.096
Cesarean section, n (%)	9 (30)	38 (32)	1.000
Male sex, n (%)	17 (57)	63 (53)	0.839
Birth weight (g)	3,026 ± 493	2,996 ± 417	0.740
Placental weight (g)	540 (490, 650)	535 (490, 610)	0.886
Neonatal complication			
Congenital malformation, n (%)	0	0	
Hypoglycemia, n (%)	2 (7)	11 (9)	1.000
Hyperbilirubinemia, n (%)	0	2 (2)	
Respiratory problem, n (%)	4 (13)	14 (12)	0.762
NICU admission, n (%)	7 (23)	26 (22)	1.000

Data are shown as mean ± standard deviation, median and inter-quartile range in the parenthesis, or number and percentage in the parenthesis.

B20w group, the subjects diagnosed before 20 weeks of gestation; A 20w group, the subjects diagnosed after 20 weeks of gestation; BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; OGTT, 75-g oral glucose tolerance test; HbA1c, glycated hemoglobin; GA, glycated albumin; HDL, high density lipoprotein; LDL, low density lipoprotein; HDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit.

in maternal age, pre-pregnancy BMI, and levels of HbA1c, GA and fasting serum C-peptide between the two subgroups. Women in the GI subgroup had higher placental weight than those in the normal subgroup.

Multiple logistic regression analysis showed that placental weight was an independent predictor for glucose

Table 2 Association of postpartum glucose tolerance and clinical factors in the B20w and A20w groups.

	B20w group			A20w group		
	Normal (n = 21)	GI (n = 9)	p	Normal (n = 83)	GI (n = 35)	p
Maternal characteristics						
Age (years)	37 (33, 39)	35 (34, 36)	0.326	34.4 ± 4.7	34.2 ± 3.3	0.759
Height (cm)	157.3 ± 5.3	159.4 ± 5.1	0.309	159.1 ± 5.1	158.2 ± 5.0	0.393
Pre-pregnancy body weight (kg)	60 (50, 75)	82 (53, 84)	0.226	54 (50, 60)	55 (48, 61)	0.675
Pre-pregnancy BMI (kg/m^2)	22.7 (21.1, 30.7)	31.6 (20.7, 32.5)	0.372	21.4 (19.7, 23.2)	21.9 (19.8, 24.1)	0.960
Nulliparous, n (%)	10 (48)	3 (33)	0.691	51 (61)	21 (60)	1.000
Family history of DM, n (%)	9 (43)	3 (33)	0.704	37 (45)	23 (66)	0.045
Smoking, n (%)	3 (14)	4 (44)	0.153	21 (25)	5 (14)	0.230
GDM diagnosis						
Gestational age at diagnosis (weeks)	15.0 ± 2.6	14.3 ± 2.0	0.459	25.7 (23.7, 30.0)	28.7 (25.4, 29.9)	0.110
OGTT plasma glucose (mg/dL)						
fasting	88.2 ± 8.4	90.9 ± 9.4	0.013	84.4 ± 8.6	83.7 ± 10.5	0.712
1h	183 (146, 210)	200 (184, 217)	0.150	174.3 ± 25.7	174.8 ± 31.9	0.930
2h	145.0 ± 32.5	169.8 ± 25.9	0.053	157 (135, 165)	162 (153, 179)	0.051
Number of abnormal values						
1 point, n (%)	12 (57)	1 (11)	0.050	55 (66)	20 (57)	0.596
2 points, n (%)	7 (33)	5 (56)		21 (25)	12 (34)	
3 points, n (%)	2 (10)	3 (33)		7 (8)	3 (9)	
HbA1c (%)	5.4 ± 0.3	5.6 ± 0.4	0.182	5.3 (5.0, 5.5)	5.2 (5.0, 5.6)	0.831
GA (%)	13.1 ± 1.3	13.3 ± 1.7	0.644	12.9 ± 1.0	13.6 ± 1.2	0.001
Fasting serum C-peptide (mg/dL)	1.40 (0.97, 1.66)	1.46 (1.11, 1.85)	0.476	1.40 (1.13, 1.83)	1.55 (1.11, 2.02)	0.631
Systolic blood pressure (mmHg)	113 ± 14	108 ± 14	0.371	109 ± 11	110 ± 10	0.458
Diastolic blood pressure (mmHg)	63 ± 9	64 ± 8	0.660	61 (57, 65)	60 (55, 67)	0.908
Serum lipid profiles						
Triglycerides (mg/dL)	180 ± 74	179 ± 106	0.977	211 (174, 282)	211 (167, 275)	0.701
HDL-cholesterol (mg/dL)	81 ± 15	77 ± 20	0.584	82 (71, 94)	82 (71, 94)	0.824
LDL-cholesterol (mg/dL)	135 (128, 151)	116 (96, 158)	0.226	149 ± 37	133 ± 40	0.051
Pregnancy outcome						
Insulin therapy during pregnancy, n (%)	11 (52)	5 (56)	1.000	18 (22)	15 (43)	0.025
HDP, n (%)	1 (5)	1 (11)	0.517	5 (6)	3 (9)	0.693
Gestational weight gain (kg)	6.1 ± 5.2	3.6 ± 7.5	0.303	8.4 ± 4.5	8.3 ± 3.1	0.799
Gestational age at delivery (weeks)	38.4 (38.0, 39.3)	38.7 (38.1, 39.0)	0.859	39.1 (38.3, 39.7)	38.9 (38.1, 39.4)	0.132
Cesarean section, n (%)	6 (29)	3 (33)	1.000	26 (31)	12 (34)	0.830
Male sex, n (%)	11 (52)	6 (67)	0.691	47 (57)	16 (46)	0.316
Birth weight (g)	2,974 (2,774, 3,136)	3,130 (3,070, 3,292)	0.094	3,037 ± 387	2,900 ± 472	0.102
Placental weight (g)	533 ± 86	632 ± 132	0.020	559 ± 98	542 ± 103	0.398
Neonatal complication						
Congenital malformation, n (%)	0	0		0	0	
Hypoglycemia, n (%)	0	2 (22)		8 (10)	3 (9)	1.000
Hyperbilirubinemia, n (%)	0	0		2 (2)	0	
Respiratory problem, n (%)	3 (14)	1 (11)	1.000	11 (13)	3 (9)	0.551
NICU admission, n (%)	4 (19)	3 (33)	0.640	18 (22)	8 (23)	1.000
OGTT after delivery (days)	59.1 ± 12.3	58.3 ± 11.4	0.867	54 (49, 65)	56 (46, 64)	0.604

Data are shown as mean ± standard deviation, median and inter-quartile range in the parenthesis, or number and percentage in the parenthesis.
B20w group, the subjects diagnosed before 20 weeks of gestation; A 20w group, the subjects diagnosed after 20 weeks of gestation; GI, glucose intolerance; BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; OGTT, 75-g oral glucose tolerance test; HbA1c, glycated hemoglobin; GA, glycated albumin; HDL, high density lipoprotein; LDL, low density lipoprotein; HDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit.

Table 3 Logistic regression analysis of predictors for postpartum glucose intolerance in the B20w and A20w groups.

	Odds ratio (95% confidence interval)	p
B20w group		
Fasting plasma glucose	0.987 (0.889-1.096)	0.803
Placental weight	1.010 (1.000-1.020)	0.049
A20w group		
Family history of DM	2.537 (1.044-6.163)	0.040
GA	1.860 (1.213-2.853)	0.004
Insulin therapy	2.406 (0.961-6.024)	0.061

B20w group, the subjects diagnosed before 20 weeks of gestation; A 20w group, the subjects diagnosed after 20 weeks of gestation; DM, diabetes mellitus; GA, glycated albumin.

intolerance in the B20w group (**Table 3**).

3. Association of postpartum glucose tolerance status and clinical factors in the A20w group

In the A20w group, postpartum OGTT revealed glucose intolerance in 35 (30%) women (GI subgroup) (IFG, 2; IGT, 31; IFG/IGT, 2) (**Table 2**).

The GI subgroup had a higher rate of family history of diabetes than the normal subgroup. GA levels in the GI subgroup were higher than those in the normal group, whereas there were no significant differences between the two subgroups in terms of pre-pregnancy BMI, fasting plasma glucose levels on OGTT, and HbA1c levels. The GI subgroup had a higher frequency of insulin therapy during pregnancy. Gestational weight gain and gestational age at delivery were similar between the two subgroups.

Multiple logistic regression analysis showed that the GA level at diagnosis of GDM and family history of diabetes were independent predictors for glucose intolerance in the A20w group (**Table 3**).

Discussion

This study showed that the 30% women who were diagnosed with GDM both before and after 20 weeks of gestation experienced glucose intolerance during the early postpartum period. Placental weight was an independent predictor for postpartum glucose intolerance in women who were diagnosed with GDM before 20 weeks of gestation, and GA levels at diagnosis of GDM and family history of diabetes were independent predictors in those who were diagnosed with GDM after 20 weeks of gestation.

Previous studies from Japan showed that the rate of abnormal glucose tolerance during the early postpartum period in patients with GDM diagnosed using the IADPSG criteria were 17-34%.[15-18] The rate of glucose intolerance in our subjects was 30%, which was relatively high. More than 30% of our subjects were referred from other hospitals in the locality, hence the severity of glucose intolerance in our subjects may be high.

Identical diagnostic criteria were applied to investigate hyperglycemic disorders at any period during pregnancy. Typical GDM occurs due to insufficient insulin production against insulin resistance in the second or third trimester of pregnancy. Insulin resistance has not yet enhanced in the early half of pregnancy. The pathophysiology of GDM diagnosed in early pregnancy is different from that of the typical GDM diagnosed in late pregnancy. In this study, we investigated subjects with GDM in the early half of pregnancy and late half of pregnancy, separately. Pre-pregnancy BMI was higher in the B20w group than in the A20w group. Being overweight or obesity is one of the risk factors for diabetes and GDM.[19] It is possible that the patients with obesity or those who were overweight in the B20w group have had glucose intolerance from pre-pregnancy, however, pre-pregnancy BMI was not a risk factor for early postpartum glucose intolerance in the B20w group. For women who were overweight, obstetricians might have been prompted to assess glucose tolerance earlier. The B20w group had a higher fasting plasma glucose levels than the A20w group. It was reported that fasting plasma glucose level decreased with increasing gestational age from the 4th week to 24th week of gestation.[20]

The rate of postpartum glucose intolerance was similar between the B20w and A20w groups. However, the risk factors for early postpartum glucose intolerance were placental weight in the B20w group, and GA levels at diagnosis of GDM and family history of diabetes in the A20w group. These results suggest that predictors for postpartum glucose intolerance vary depending on the time of diagnosis of GDM, when using the same diagnostic criteria in both early and late pregnancy. Data regarding recommended cut-off values of OGTT results to identify hyperglycemic disorders in early pregnancy are

still limited. Therefore, further investigations are needed to define the diagnostic criteria for early GDM.

Women with a history of GDM have an increased risk of developing type 2 diabetes. High BMI, family history of diabetes, non-Caucasian ethnicity, advanced maternal age, early diagnosis of GDM, elevated fasting glucose, increased HbA1c, use of insulin during pregnancy, multiparity, hypertensive disorders in pregnancy, and preterm labor were associated with a future risk of type 2 diabetes in a systematic review and meta-analysis.[21] Moreover, some women with GDM show glucose intolerance from the early postpartum period. Recent studies reported that the risk factors of early postpartum glucose intolerance in women with GDM were specific ethnicity, HbA1c level at diagnosis of GDM, glucose levels in OGTT, fasting plasma glucose, BMI, polycystic ovary syndrome, and decreased β-cell function.[22-27] In Japanese women with GDM, diagnosed using the IADPSG criteria, the 1h- and 2h-glucose levels in diagnostic OGTT, insulinogenic index, insulin secretion-sensitivity index-2, and insulin treatment during pregnancy predicted early postpartum glucose intolerance.[15-18] Our study is the first to show that GA level at the time of GDM diagnosis was a predictor of early postpartum glucose intolerance. The association between GA level and postpartum glucose intolerance was yet to be investigated.

GA is one of the biomarkers used to evaluate glycemic control. At present, HbA1c is used widely in clinical practice as a gold standard index of glycemic control. HbA1c reflects the mean glycemic status over the previous two months, while GA reflects the mean glycemic status over the previous three weeks; this difference is associated with the difference in life spans of erythrocyte and albumin.[28] GA provides more rapid and marked indication of the change in glycemic status than HbA1c. In addition, it has been known that the HbA1c level increases significantly at the latter stage of pregnancy because of the increased demand for iron, while GA remains stable throughout pregnancy.[29, 30] A recent study showed that the GA level during late pregnancy was significantly higher in diabetes mothers whose infants had neonatal complications.[31] On the basis of these results, the Japanese Society of Diabetes and Pregnancy has recommended measurement of GA during pregnancy to prevent perinatal complications in women with glycemic disorders.

In the B20w group, placental weight was a predictor of early postpartum glucose intolerance. Increased placental weight has been reported in pregnant women with GDM.[32, 33] Increased placental weight was associated with maternal insulin resistance[34] and insulin secretary response in early pregnancy.[35] Furthermore, animal experiments have shown that glucose injections in early pregnancy increased placental weight.[36] These findings suggest that maternal metabolic status in early pregnancy affects placental growth, therefore, women in the B20w group may have hyperglycemia and hyperinsulinemia due to insulin resistance from pre-pregnancy or early pregnancy.

The limitations of this study include the relatively small sample size and the possibility of selection bias, because 30% of our subjects were referred from other hospitals. In addition, it was not verified whether all subjects in the A20w group were free from hyperglycemic disorder before 20 weeks of gestation. Another limitation is that breast-feeding, which may affect glucose tolerance, was not investigated in this study.

In conclusion, 30% of patients with GDM had glucose intolerance in the early postpartum period. GA level at diagnosis of GDM was associated with early postpartum glucose intolerance among women diagnosed with GDM after 20 weeks of gestation. GA may be a useful indicator not only for achievement of metabolic control during pregnancy but also for predicting postpartum glucose intolerance.

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Other authors declare that they have no conflict of interest.

References

1. Bellamy L, Casas J-P, Hingorani AD et al: Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 373: 1773−1779, 2009
2. Kim C, Newton KM, Knopp RH: Gestational diabetes and the incidence of type 2 diabetes. A systematic review. Diabetes Care 25: 1862−1868, 2002
3. Japan Society of Obstetrics and Gynecology/Japan Association of Obstetricians and Gynecologists: Ninshintounyoubyou, ninshinchunoakirakanatounyoubyou, narabini tounyoubyougappeininpu no kanri, bunbenha? *In* Guideline for Obstetrical Practice in Japan 2020, pp25−28, Japan Society of Obstetrics and Gynecology, Tokyo (2020)
4. American Diabetes Association: 14. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes-2020. Diabetes Care 43 (Suppl 1): S183−S192, 2020
5. Lawrence JM, Black MH, Hsu J-W et al: Prevalence and timing of postpartum glucose testing and sustained glucose dysregulation after gestational diabetes mellitus. Diabetes Care 33: 569−576, 2010
6. Kwong S, Mitchell RS, Senior PA et al: Postpartum diabetes screening: Adherence rate and the performance of fasting plasma glucose versus oral glucose tolerance test. Diabetes Care 32: 2242−2244, 2009
7. Almario CV, Ecker T, Moroz LA et al: Obstetricians seldom provide postpartum diabetes screening for women with gestational diabetes. Am J Obstet Gynecol 198: 528.e1−528.e5, 2008
8. Hunt KJ, Conway DL: Who returns for postpartum glucose screening following gestational diabetes mellitus? Am J Obstet Gynecol 198: 404.e1−404.e6, 2008
9. Russell MA, Phipps MG, Olson CL et al: Rates of postpartum glucose testing after gestational diabetes mellitus. Obstet Gynecol 108: 1456−1462, 2006
10. Kim C, Tabaei BP, Burke R et al: Missed opportunities for type 2 diabetes mellitus screening among women with a history of gestational diabetes mellitus. Am J Public Health 96: 1643−1648, 2006
11. Morikawa M, Yamada T, Yamada T et al: Change in the number of patients after the adoption of IADPSG criteria for hyperglycemia during pregnancy in Japanese women. Diabetes Res Clin Pract 90: 339−342, 2010
12. Jang HC, Yim C-H, Han KO et al: Gestational diabetes mellitus in Korea: prevalence and prediction of glucose intolerance at early postpartum. Diabetes Res Clin Pract 61: 117−124, 2003
13. McClean S, Farrar D, Kelly CA et al: The importance of postpartum glucose tolerance testing after pregnancies complicated by gestational diabetes. Diabet Med 27: 650−654, 2010
14. World Health Organization: Report of a WHO Consultation: Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. World Health Organization Department of Noncommunicable Disease Surveillance, Geneva (1999). http://www.staff.ncl.ac.uk/philip.home/who_dmc.htm (Accessed August 4, 2020)
15. Kugishima Y, Yasuhi I, Yamashita H et al: Risk factors associated with abnormal glucose tolerance in the early postpartum period among Japanese women with gestational diabetes. Int J Gynaecol Obstet 129: 42−45, 2015
16. Katayama H, Tachibana D, Hamuro A et al: Sustained decrease of early-phase insulin secretion in Japanese women with gestational diabetes mellitus who developed impaired glucose tolerance and impaired fasting glucose postpartum. Jpn Clin Med 6: 35−39, 2015
17. Kojima N, Tanimura K, Deguchi M et al: Risk factors for postpartum glucose intolerance in women with gestational diabetes mellitus. Gynecol Endocrinol 32: 803−806, 2016
18. Kasuga Y, Miyakoshi K, Tajima A et al: Clinical and genetic characteristics of abnormal glucose tolerance in Japanese women in the first year after gestational diabetes mellitus. J Diabetes Investig 10: 817−826, 2019
19. Benhalima K, Mathieu C, Damm P et al: A proposal for the use of uniform diagnostic criteria for gestational diabetes in Europe: an opinion paper by the European Board & College of Obstetrics and Gynaecology (EBCOG). Diabetologia 58: 1422−1429, 2015
20. Zhu W-W, Yang H-X, Wei Y-M et al: Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. Diabetes Care 36: 586−590, 2013
21. Rayanagoudar G, Hashi AA, Zamora J et al: Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic review and meta-analysis of 95,750 women. Diabetologia 59: 1403−1411, 2016
22. Benhalima K, Jegers K, Devlieger R et al: Glucose intolerance after a recent history of gestational diabetes based on the 2013 WHO criteria. PLoS One 11: e 0157272, 2016. doi: 10.1371/journal.pone.0157272
23. Shin N-R, Yoon S-Y, Cho GJ et al: A Korean multicenter study of prenatal risk factors for overt diabetes during the postpartum period after gestational diabetes mellitus. Int J Gynecol Obstet 132: 342−346, 2016
24. Monroy G, Tundidor D, Orellana I et al: Antenatal oral glucose tolerance test in women with gestational diabetes mellitus: fasting plasma glucose is the best predictor of both large for-gestational-age newborns and postpartum glucose tolerance. Minerva Endocrinol 42: 311−317, 2017
25. Capula C, Chifari E, Vero A et al: Prevalence and predictors of postpartum glucose intolerance in Italian

women with gestational diabetes mellitus. Diabetes Rer Clin Pract 105: 223−230, 2014
26. Kwak SH, Choi SH, Jung HS et al: Clinical and genetic risk factors for type 2 diaebetes at early or late post partum after gestational diabetes mellitus. J Clin Endocrinol Metab 98: E744−E752, 2013
27. Saisho Y, Miyakoshi K, Tanaka M et al: Antepartum oral disposition index as a predictor of glucose intolerance postpartum. Diabetes Care 35: e32, 2012
28. Freitas PAC, Ehlert LR, Camargo JL: Glycated albumin: a potential biomarker in diabetes. Arch Endocrinol Metab 61: 296−304, 2017
29. Hashimoto K, Osugi T, Noguchi S et al: A1C but not serum glycated albumin is elevated because of iron deficiency in late pregnancy in diabetic women. Diabetes Care 33: 509−511, 2010
30. Hiramatsu Y, Shimizu I, Omori Y et al: Determination of reference intervals of glycated albumin and hemoglobin A1c in healthy pregnant Japanese women and analysis of their time courses and influencing factors during pregnancy. Endocr J 59: 145−151, 2012
31. Sugawara D, Sato H, Ichihashi K et al: Glycated albumin level during late pregnancy as a predictive factor for neonatal outcomes of women with diabetes. J Matern Fetal Neonatal Med 31: 2007−2012, 2018
32. Lao TT, Lee C-P, Wong W-M: Placental weight to birthweight ratio is increased in mild gestational glucose intolerance. Placenta 18: 227−230, 1997
33. Kucuk M, Doymaz F: Placental weight and placental weight-to-birth weight ratio are increased in diet- and exercise-treated gestational diabetes mellitus subjects but not in subjects with one abnormal value on 100-g oral glucose tolerance test. J Diabetes Complications 23: 25−31, 2009
34. Tanaka K, Yamada K, Matsushima M et al: Increased maternal insulin resistance promotes placental growth and decreases placental efficiency in pregnancies with obesity and gestational diabetes mellitus. J Obstet Gynaecol Res 44: 74−80, 2018
35. O'Tierney-Ginn P, Presley L, Myers S et al: Placental growth response to maternal insulin in early pregnancy. J Clin Endocrinol Metab 100: 159−165, 2015
36. Ericsson A, Säljö K, Sjöstrand E et al: Brief hyperglycaemia in the early pregnant rat increases fetal weight at term by stimulating placental growth and affecting placental nutrient transport. J Physiol 581: 1323−1332, 2007