

Study on long-term prognosis of women with a history of gestational diabetes mellitus in Tsugaru
District, Aomori Prefecture

GDM PostPartum Aomori Prefecture Study (GDM PPAP Study)

(青森県津軽地域における妊娠糖尿病既往女性の長期予後調査 GDM-PPAP Study)

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ABSTRACT

Objectives: This study aimed to clarify the health status of women with gestational diabetes mellitus (GDM) in Tsugaru District, Aomori Prefecture, Japan, and provide information for establishing a long-term follow-up system for women with a history of GDM.

Methods: Questionnaires were mailed to women diagnosed with GDM who gave birth between 2006 and 2015 at four general hospitals in Tsugaru District. Subjects were grouped according to progression or non-progression of GDM to type 2 diabetes mellitus (DM), and clinical characteristics between both groups during pregnancy were compared. A health survey was performed in women with GDM.

Results: There were a total of 10,681 deliveries, and 516 women were diagnosed with GDM. Out of those, 452 women were eligible for the study. The questionnaires were mailed to them, and 227 women returned the questionnaire. The number of women with progression of GDM to DM was 14, but only 5 out of those returned the questionnaires. Although the current age of women who developed DM was under 40 years old, women with a history of GDM who had not had health checkups were significantly younger than

those who had had health checkups, with a larger proportion being younger than 40 years.

Conclusions: Women with a history of GDM of less than 40 years old in Aomori Prefecture had less opportunity of their health checkups. Therefore, it is preferable to provide medical checkup recommendation system for the women with a history of GDM even if the current age is under 40 years old.

Key word: Gestational diabetes mellitus, long-term prognosis, postpartum follow-up

INTRODUCTION

Women with a history of gestational diabetes mellitus (GDM) are at high risk for developing diabetes mellitus (DM) and other lifestyle-related diseases such as cardiovascular disease later in life¹⁻⁴⁾. In Japan, approximately 20% of women with a history of GDM developed DM within 5 years after delivery, and the figure rose to 30% after 10 years ^{5, 6)}. Although the American Diabetes Association, American College of Obstetricians and Gynecologists, and National Institute for Health and Care Excellence emphasize long-term follow-up and postpartum intervention with respect to lifestyle-related diseases, they merely indicate necessity of follow-up examinations at intervals of 1-3 years ⁷⁻¹⁰⁾. The American Diabetes Association recommends having follow-up examinations at 4-12 weeks after delivery, but the implementation rate is low ¹⁰⁻¹⁶⁾, and the long-term follow-up rate is still low ¹⁷⁻¹⁹⁾. The Japan Society of Obstetrics and Gynecology only recommends follow-up examination at 6-12 weeks after delivery, and no long-term follow-up system has been established ²⁰⁾.

The residents of Aomori Prefecture, located at the northern part of Honshu Island of Japan, have the shortest life expectancy and a short healthy life expectancy, which would

be attributed to a high mortality rate due to advanced lifestyle-related diseases such as DM, stroke and cardiovascular diseases²¹⁻²⁴). As one of the measures to reduce the high mortality associated with lifestyle-related diseases, early detection and intervention in women carrying risk factors of the diseases are well documented ^{24, 25}).

Although it is well recognized that women with GDM possibly develop type 2 DM and early intervention reduces the progression of GDM to type 2 DM ^{7, 26, 27}), no postpartum follow-up system has been reported so far. This study aimed to clarify the health status of women with a history of GDM in Tsugaru District, Aomori Prefecture, Japan, and provide useful information for establishing a postpartum follow-up system in the near future.

METHODS

Study design and patient population

The GDM postpartum Aomori Prefecture (GDM-PAP) study is an observational, retrospective, cross-sectional study. The subjects comprised women with GDM who gave birth between 2006 and 2015 at one of the four general hospitals in Tsugaru District. Diagnosis of GDM was confirmed from medical records and performed using new diagnostic criteria; being positive for at least one of the following items in the 75-g oral glucose tolerance test (OGTT) indicated GDM: (i) fasting plasma glucose (FPG) of ≥ 92 g/dL, (ii) 1-h plasma glucose (PG) of ≥ 180 mg/dL, and (iii) 2-h PG of ≥ 153 mg/dL ²⁸).

The exclusion criteria were as follows: (i) history of overt diabetes during pregnancy, (ii) suspected postpartum GDM, (iii) having returned to hometowns (i.e., in Tsugaru District) to give birth, and (iv) being a non-Japanese.

Data collection and classification

Because the diagnostic criteria for GDM were revised in 2010, GDM diagnosed before 2010 was re-diagnosed by the new criteria using the 75-g OGTT, and those who

met the new criteria were selected.

The parameters evaluated in this study were age at delivery, height, body weight before pregnancy, body mass index (BMI) before pregnancy, parity, OGTT results at diagnosis, hemoglobin A1c at diagnosis, the week number of pregnancy at GDM diagnosis, family history of type 2 DM, presence/absence of chronic hypertension, treatment details, presence/absence of hypertensive disorders of pregnancy, and postpartum 75-g OGTT results. The data of hemoglobin A1c since April 1, 2012, were used in accordance with the National Glycohemoglobin Standardization Program (NGSP); for data before that date, the NGSP values were calculated using a conversion table ²⁹⁾. Parents and siblings were considered in evaluating family history of type 2 DM. Postpartum OGTT results were categorized as follows: (i) normal glucose tolerance (NGT) for FPG of <100 mg/dL and 2-h PG of <140 mg/dL, (ii) impaired fasting glucose (IFG) for FPG of 100-125 mg/dL, (iii) impaired glucose tolerance (IGT) for 2-h PG of 140-199 mg/dL, and (iv) DM for 2-h PG of \geq 200 mg/dL. Women with GDM were tested postpartum OGTT at 6-12 weeks after delivery.

The subjects were mailed with questionnaires that had items to select and sections to

complete but did not need signing, as well as explanatory documents about the study. The period for returning the questionnaires, by post, was January to March 2017. Questionnaire items included age, body weight, whether the subject had had health checkups, health checkup location, presence of DM, presence of hypertension, family history of DM, whether the subject understood the risk of progression from GDM to DM, subject's interest in or concern about health, alcohol consumption level (consumption frequency, drink type, and quantity consumed per occasion), smoking level, and physical activity. It was calculated whether a consumption level of 20 g/day of pure alcohol was sufficient to increase the risk of lifestyle-related diseases ³⁰). Physical activity was determined using the short version of the International Physical Activity Questionnaire (IPAQ), which had categories based on the scoring protocol ³¹⁻³³).

Statistical analyses

Comparisons between subjects who did and did not return the questionnaire and subjects who did and did not develop DM were performed using Mann-Whiney-U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. We used the number of deliveries to assess the characteristics during pregnancy

and the number of women to assess the questionnaire.

Significant difference was considered at $P < 0.05$. All statistical analyses were carried out using JMP version 13.0.

Ethical considerations

This study was approved by the ethics committees of Hirosaki University and the four hospitals that collaborated with the study. Among women who were mailed with questionnaires, the act of returning the questionnaire was considered informed consent.

Women who did not return the questionnaires or whose addresses were unknown were handled as having been provided with information about use of patient data during pregnancy and were given explanations.

RESULTS

From 2006 to 2015, there were 10,681 deliveries at the four hospitals, and 516 women with 537 deliveries met the new diagnostic criteria for GDM. Out of those, 64 women with 67 deliveries were excluded as they resided outside Aomori Prefecture or had overt DM, and questionnaires were mailed to 452 subjects (470 deliveries) (Figure 1). Based on the hospitals' medical records, 14 subjects were confirmed to have developed type 2 DM, while 438 did not develop DM.

Table 1 shows basal data during pregnancy in subjects who developed type 2 DM (DM women, $n = 14$) and those who did not (non-DM women, $n = 456$). DM women had significantly long postpartum period after delivery, high pre-pregnant BMI scores and high serum glucose levels according to the 75-g OGTT compared to non-DM women. Additionally, DM women showed a significantly high incidence of 2-point abnormal glucose tolerance in response to the 75-g OGTT compared to non-DM women. No differences were found for current age, family history or associated chronic hypertension between both women, but DM women had a significantly high incidence of hypertensive disorders during pregnancy.

Postpartum OGTT results were recorded in 9 DM women and 236 non-DM women.

As shown in Table 2, DM women had a significantly high incidence of abnormal glucose tolerance patterns such as IFG, IGT, and DM compared to non-DM women.

Out of 452 subjects mailed with the questionnaires, 227 returned them with answers (response rate, 50.2%). Table 3 shows the characteristics of the 227 subjects.

The median postpartum period was 4 years. The proportion of subjects who had had health checkups was 70%, however in subjects less than 40 years old, the proportion decreased to 62%. The number of health checkups at the workplace was also high. The proportion of subjects who were aware of the risk of progression from GDM to DM was 87%. The proportion of those whose alcohol consumption was sufficient to increase the risk of lifestyle-related diseases was 16% (37 of 227 subjects), and the proportion of habitual smokers was 18% (41 of 227). Moreover, the proportion of subjects who exercised habitually (IPAQ category 2 or higher) was 47%. Out of 5 subjects who developed DM, 3 subjects took oral hypotensive agents.

Excluding the 5 subjects who developed DM, comparisons in 222 subjects were made between those who had and had not had health checkups (Table 4). Women who had not

had health checkups were significantly younger than those who had had health checkups, with a larger proportion being younger than 40 years. There was no difference in BMI, but 41% of subjects who had not had health checkups were obese ($\text{BMI} \geq 25$). A significantly larger proportion of subjects who had not had health checkups were smokers, and a relatively large proportion (9%) lacked interest in their health. The proportion of subjects who took little or no exercise (IPAQ category 1) was significantly higher in women who had had checkups.

DISCUSSION

This is a retrospective investigation of the characteristics during pregnancy and the health status of women with a history of GDM who gave birth in Tsugaru District. As reference, among 13,327 deliveries in Tsugaru District in the 5-year period between 2011 and 2015, a total of 6,722 (50%) were at the four hospitals where this study was conducted.

Aomori Prefecture has the shortest life expectancy among any Japanese prefectures, which could be attributed to a high mortality rate due to advanced lifestyle-related diseases ^{21, 22, 24}). This study was therefore conducted based on the premise that postpartum follow-up of women with a history of GDM is important for their health care

and prevention of developing DM and lifestyle-related diseases that might deteriorate their quality of life in Aomori prefecture.

The number of subjects who developed DM within 10 years after delivery was only 14, but this group had a high degree of obesity and elevated OGTT results at GDM diagnosis and longer postpartum period after delivery.

In a report based on previous studies, the possibility has been suggested that women with a history of GDM develop DM within 5 years after delivery ¹⁾ ; in Japan, 20% of women with a history of GDM developed DM within 5 years ^{5, 6)}. However, in the present study, only 14 out of 452 subjects (3.1%) developed DM. This difference can be explained by the low rate of GDM (5%) in Aomori Prefecture, the short period after delivery covered by this study, and probability that some of the subjects who did not return the questionnaires and/or had not had health checkups had developed DM. Other possibility of the difference is that because the previous studies ^{5, 6)} targeted only high risk women with GDM who might progress to DM, a selection bias might arise. In general, the result that 20% of women with a history of GDM developed DM within 5 years after

delivery seems rather higher than expected in population of Japanese women with a history of GDM.

There have been various reports about the risk of developing DM after GDM, and high FPG, obesity, insulin treatment during pregnancy, postpartum IGT, delivery age under 35 years old and so on have been suggested as contributory factors ^{5, 6, 34-39}). The findings in the present study also imply that particular care is needed in women who are obese, younger, positive for two or more abnormal values of OGTT at diagnosis, and/or who have early postpartum abnormal glucose tolerance. Additionally, even in subjects that apparently did not develop DM, approximately 30% had postpartum OGTT results categorized as IFG, IGT, or DM; thus, the possibility is suggested that this group included subjects who did develop DM.

The proportion of subjects who had undergone health checkups was 70%, and this proportion fell to 62% in subjects who were younger than 40 years old. In contrary, 49 (74%) of 66 subjects who did not take health checkups were younger than 40 years.

The low rate of having regular health checkup in the generation of less than 40 years old after delivery might be due to various reasons as follows: poor communication

between women and health-care providers, limited understanding of the importance of follow-up ¹²⁾, misunderstanding that GDM would not progress to DM after delivery, and full-time work looking after the infant ¹⁴⁾.

This study showed that although 87% of subjects diagnosed with GDM during pregnancy were aware of the risk of developing DM in the future, women of less than 40 years old did not take their sufficient health care. In Japan, Health Insurance Act recommends special medical checkups of people of more than 40 years old. On the other hand, people of less than 40 years old can receive only general health diagnosis by local government. Thus, the present low rate of having regular health checkup in the generation of less than 40 years old after delivery may result from such a Japanese social system concerning health checkups. Waguri reported that the age of less than 35 years old at delivery was a risk factor to progress GDM to DM ^{5, 6)}, and this study also showed that the age at delivery in DM women was younger than in non-DM women. Therefore, it is preferable to provide medical checkup recommendation system for the women with a history of GDM even if the present age is under 40 years old.

In Japan, a long-term follow-up system for women with a history of GDM has not

been established. Specialty outpatient clinic for following up women with a history of GDM has opened at Hirosaki University Hospital since 2014 ^{40, 41)}. Figure 2 showed our procedure of following up women with a history of GDM. First, women with GDM undergo OGTT at 6-12 weeks after delivery. According to the result, follow-up interval is decided. Date to visit our clinic is set on their child's birthday and the reminder letter will be sent before one month of visit. Blood pressure, body weight, 75g OGTT and biochemical test are examined every time. Uterine cancer screening, transvaginal ultrasound examination and nutrition guidance will be also planned.

Family physicians and internists bear postpartum GDM follow-up in United States of America (USA) and United Kingdom (UK), but long-term follow-up system for postpartum GDM has not been organized in both countries ^{17, 19, 42, 43)}. The problem in Aomori Prefecture's medical practice is that the number of Obstetricians is not sufficient although the area of the prefecture is large. Thus, it is more reasonable that long-term follow-up of women with a history of GDM is performed along with the internists.

This study has two main limitations. It involved a questionnaire-based survey; thus, women whose addresses were unknown or who did not return the questionnaires were

not evaluated, and among subjects who returned the questionnaires, only few developed type 2 DM. The data on lifestyle and health status related only to subjects who returned their questionnaires; therefore, a sampling bias existed.

In conclusion, women with a history of GDM of less than 40 years old in Aomori Prefecture had had less opportunity of their health checkups. Thus, it is preferable to provide medical checkup recommendation system for the women with a history of GDM even if the current age is under 40 years old. Long-term follow-up of women with a history of GDM is important for their health care and prevention of developing DM and lifestyle-related diseases that might deteriorate their quality of life in Aomori prefecture.

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FIGURE LEGENTD

Figure 1: Flowchart of women with GDM in Tsugaru District

Figure 2: How to follow-up women with a history of GDM at Department of Obstetrics
and Gynecology, Hirosaki University.

Table 1. Basal characteristics of pregnancy between women with progression of GDM to type 2 DM (DM women) and women with no progression to type 2 DM (non-DM women)

	DM women n = 14	Non-DM women n = 456	p-value
Delivery age (years)	31 (28-35)	33 (29-37)	0.17
Current age(years)	37(33-41)	38(34-42)	0.79
Postpartum period (years)	6.5(4-8.3)	4(3-6)	0.0093
Pre-pregnant BMI (kg/m ²)	30.1 (24.9-37.0)	23.0 (20.1-27.6)	0.0002
Pre-pregnant BMI ≥ 25 (n, %)	11 (79%)	173 (38%)	0.0022
OGTT at diagnosis	FPG (mg/dL)	100 (88-107)	<0.0001
	1-h PG (mg/dL)	192 (185-215)	0.0003
	2-h PG (mg/dL)	171 (150-196)	0.026
OGTT at diagnosis of ≥2 points (n, %)	12 (86%)	132 (29%)	<0.0001
Diagnosis (weeks)	16 (12-27)	20 (13-30)	0.27
HbA1c at diagnosis (NGSP, %)	6.1 (5.5-6.2) (n = 9)	5.4 (5.2-5.7) (n = 294)	0.0038
Primiparas (n, %)	6 (43%)	188 (41%)	1.0
Family history (n, %) (parents/ siblings)	6 (43%)	150 (33%)	0.57
Chronic HT (n, %)	1 (7%)	14 (3%)	0.37
Insulin use (n, %)	3 (21%)	28 (6%)	0.058
HDP (n, %)	4 (29%)	30 (7%)	0.014
Delivery (weeks)	39 (38-40)	39 (38-40)	0.60
Postpartum OGTT (n, %)	9 (64%)	236 (52%)	0.35

GDM: gestational diabetes mellitus; DM: diabetes mellitus; BMI: body mass index; FPG: fasting plasma glucose; PG: plasma glucose; OGTT: 75-g oral

glucose tolerance test; HbA1c: hemoglobin A1c; NGSP: National Glycohemoglobin Standardization Program units; HT: hypertension; HDP: hypertensive disorder of pregnancy.

Table 2. Postpartum OGTT results between women with progression of GDM to type 2 DM (DM women) and women with no progression to type 2 DM (non-DM women)

Postpartum OGTT results	DM women n = 9	non-DM women n = 236	p-value
NGT (n, %)	2 (22%)	167 (71%)	<0.001
IFG/IGT type (n, %)	5 (56%)	65 (28%)	
DM type (n, %)	2 (22%)	4 (2%)	
IFG/IGT or DM type (n, %)	7 (78%)	69 (29%)	0.0045
FPG (mg/dL)	97 (88-102)	86 (81-92)	0.011
1-h PG (mg/dL)	165 (133-199)	145 (123-172)	0.22
2-h PG (mg/dL)	141 (106-182)	123 (104-141)	0.19

OGTT: 75-g oral glucose tolerance test; GDM: gestational diabetes mellitus; DM: diabetes mellitus; NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; FPG: fasting plasma glucose; PG: plasma glucose.

Table 3. Characteristics of women who answered the questionnaires

		Median (interquartile range) or n (%)
Answer (n)		227
Age (years)		38 (34-42)
Postpartum period (years)		4(3-6)
Age ≥ 40 years (n, %)		93 (41%)
Current BMI (kg/m²) (n = 220)		23.5 (20.2-27.3)
Current BMI ≥ 25 (n = 220) (n, %)		83 (38%)
Underwent medical checkup	All age (n, %)	159 (70%)
	Age < 40 years (n, %)	83 (62%)
	Age ≥ 40 years (n, %)	76 (82%)
	Company (n, %)	115 (74%)
Place of medical checkup (n = 159)	Cities (n, %)	34 (22%)
	Personal (n, %)	3 (2%)
	Another (n, %)	7 (4%)
T2DM (n, %)		5 (2%)
Diagnosis age of T2DM (n = 5) (years)		36 (32-38)
T2DM treatment	Diet (n, %)	2 (40%)
	OHA (n, %)	3 (60%)
HT (n, %)		8 (4%)
Family history (parents/siblings)(n, %)		103 (46%)
Interest in health (n = 225) (n, %)		217 (96%)
Knowledge of GDM risks (n = 202) (n, %)		179 (87%)
Alcohol drinking and risk of metabolic syndrome (n, %)		37 (16%)
Smoking (n, %)		41 (18%)
IPAQ	Category 1 (n, %)	120 (53%)
	Category 2 (n, %)	62 (27%)
	Category 3 (n, %)	45 (20%)

BMI: body mass index; T2DM: type 2 diabetes mellitus; HT: hypertension; GDM: gestational diabetes

コメントの追加 [A1]: Please check if the edit conveys the intended meaning.

mellitus; IPAQ: International Physical Activity Questionnaire; OHA: oral hypoglycemic agent.

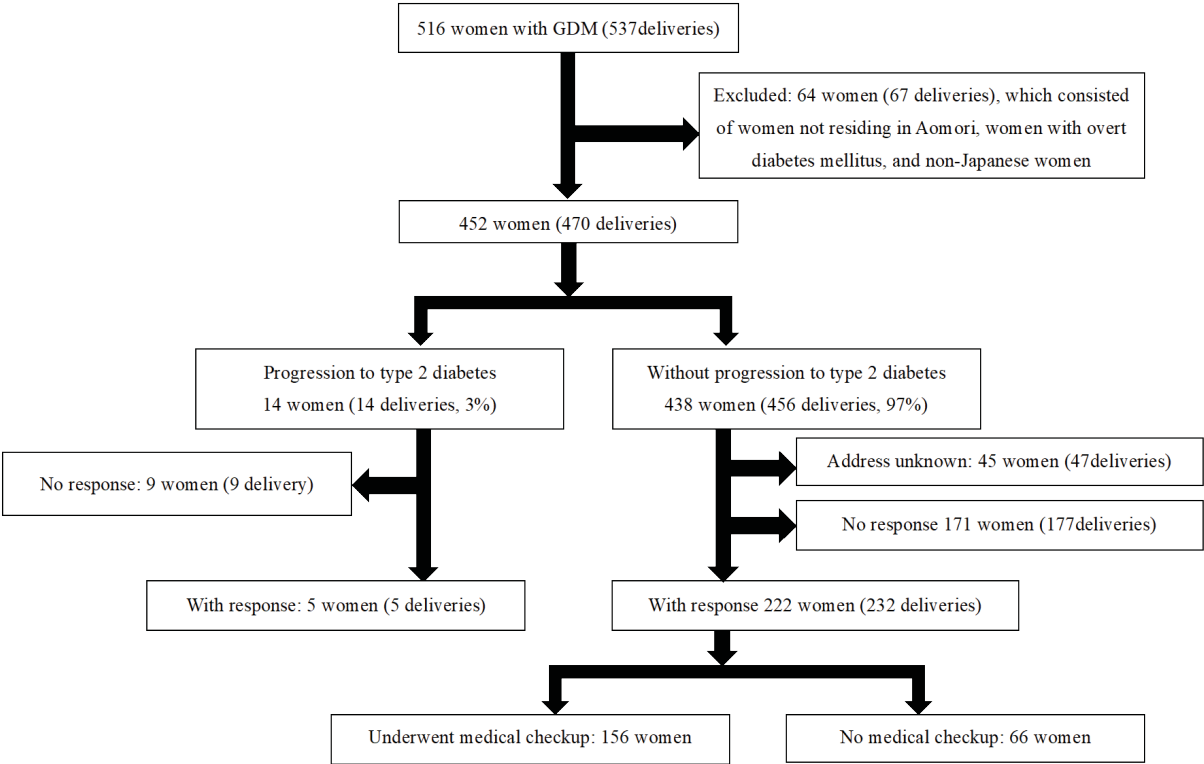
Table 4. Questionnaire answers compared between women who took a medical checkup and women who did not take a checkup, excluding 5 DM women

	Took a medical checkup (n = 156)	Did not take a medical checkup (n = 66)	p-value
Current age (years)	39 (35-42)	37 (33-40)	0.0095
Postpartum period (years)	4(3-6)	4(3-6)	0.37
Age < 40 years (n, %)	82 (53%)	49 (74%)	0.0027
Current BMI (kg/m ²)	23.2 (20.3-26.4) (n = 152)	23.8 (19.8-27.9) (n = 63)	0.68
BMI ≥ 25 (n, %)	52 (34%) (n = 152)	26 (41%) (n = 63)	0.33
Family history (n, %)(parents/siblings)	69 (44%) (n = 156)	33 (51%) (n = 65)	0.37
Interest in health (n, %)	155 (99%) (n = 156)	58 (91%) (n = 64)	0.0027
Knowledge of GDM risks (n, %)	127 (90%) (n = 141)	52 (85%) (n = 61)	0.32
Smoking (n, %)	22 (14%)	19 (29%)	0.01
Alcohol drinking and risk of metabolic syndrome (n, %)	29 (19%)	8 (12%)	0.24
IPAQ	Category 1 (n, %)	27 (41%)	0.027
	Category 2 (n, %)	19 (29%)	
	Category 3 (n, %)	20 (30%)	
IPAQ category 2 or 3 (n, %)	66 (42%)	39 (59%)	0.022

DM: diabetes mellitus; BMI: body mass index; GDM: gestational diabetes mellitus; IPAQ: International Physical Activity Questionnaire.

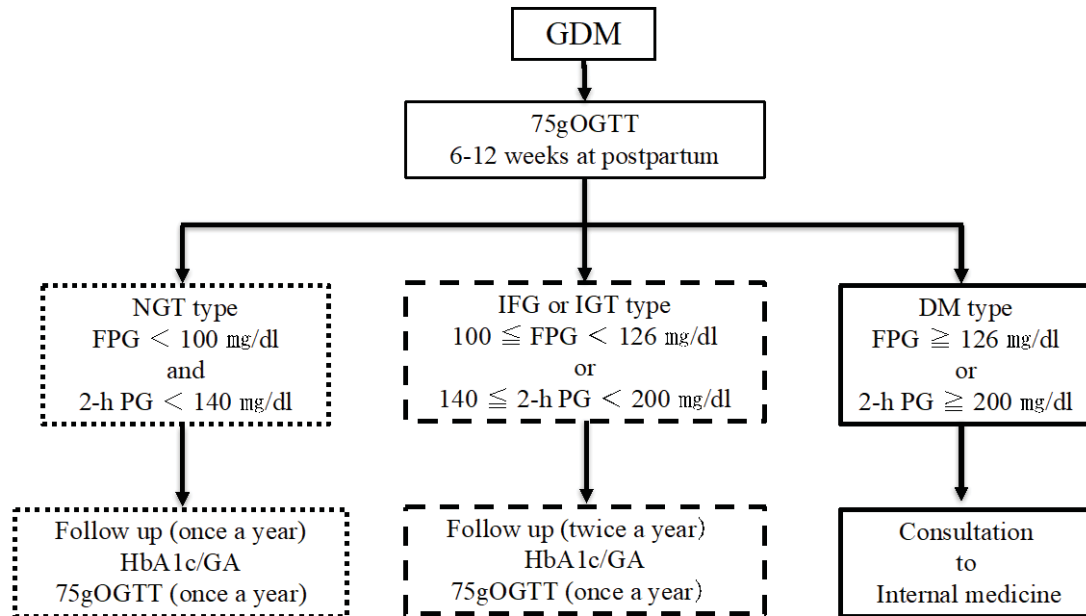
コメントの追加 [A1]: Please check if the edit conveys the intended meaning.

Figure1.



※GDM: gestational diabetes mellitus.

Figure 2.



※GDM: gestational diabetes mellitus; 75g OGTT: 75g oral glucose tolerance test; NGT: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus; FPG: fasting plasma glucose; 2-h PG: 2hour plasma glucose; HbA1c: hemoglobin A1c; GA: glycoalbumin.