

[CASE REPORT]

Type 1 Diabetes Mellitus Diagnosed during Follow-up of Gestational Diabetes Mellitus in the Early Postpartum Period

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Abstract:

A 27-year-old woman with a history of gestational diabetes mellitus (GDM) developed type 1 diabetes mellitus (T1D) in the early postpartum period. Women with a history of GDM are at an increased risk of developing T1D, which is rarer than type 2 diabetes mellitus. A postpartum follow-up 75-g oral glucose tolerance test and the measurement of glutamic acid decarboxylase autoantibodies aided in the early detection of T1D in this patient. Careful attention should be paid to women with a history of GDM who exhibit clinical features suggestive of future development of T1D.

Key words: gestational diabetes mellitus, type 1 diabetes mellitus, slowly progressive type 1 diabetes mellitus, postpartum

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Introduction

Gestational diabetes mellitus (GDM) is defined by the onset or first recognition of abnormal glucose tolerance during pregnancy that is less severe than overt diabetes mellitus (1). In a systematic review and meta-analysis, women with a history of GDM had at least a seven-fold increased risk of developing type 2 diabetes mellitus (T2D) during the postpartum period compared to those who were normoglycemic during their pregnancies (2). Women with GDM are predisposed to developing type 1 diabetes mellitus (T1D) in the postpartum period if they have pancreatic beta-cell autoantibodies (3-5).

The prevalence of glutamic acid decarboxylase autoantibodies (GADA) in women with GDM in a previous or current pregnancy is reported to be 0-9.5% (3-15). T1D is a chronic autoimmune disease, and the pre-diabetic stage can exist concurrently with immunologic abnormalities (16). Pregnant women with an abnormal glucose tolerance can be

diagnosed with GDM even if they are in the pre-diabetic stage of T1D, which may result in patients with T1D being overlooked. The early diagnosis and insulin therapy for T1D help prevent acute complications, such as diabetic ketoacidosis.

We herein report a patient with T1D diagnosed using a 75-g oral glucose tolerance test (OGTT) during follow-up of GDM in the postpartum period.

Case Report

A 27-year-old woman, gravida 2 para 0, with a family history of diabetes mellitus was referred to our hospital's obstetrics and gynecology department for GDM management at 27 weeks' gestation. She was diagnosed with GDM after the first 75-g OGTT based on plasma glucose levels of 73 mg/dL, 193 mg/dL, and 173 mg/dL at fasting, 1-hour, and 2-hour post-glucose load, respectively. She was prescribed nutritional therapy of 1,900 kcal per day, consisting of three small-to-moderate sized meals and three snacks and

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Table 1. Laboratory Results on Admission.

| | Reference | | | Reference | |
|--|-----------|------------|---------------------------------------|-----------|-------------|
| Diabetes | | | Blood Count | | |
| Glucose (mg/dL) | 78 | 73-109 | White blood cell (μ L) | 5,100 | 3,300-8,600 |
| Hemoglobin A1c (%) | 5.8 | 4.9-6.0 | Red blood cell ($\times 10^4/\mu$ L) | 386 | 386-492 |
| Urinary C-peptide (μ g/day) | 13.3 | 18.3-124.4 | Hemoglobin (g/dL) | 11.7 | 11.6-14.8 |
| IA-2 antibody (U/mL) | 8.2 | <0.4 | Platelet ($\times 10^4/\mu$ L) | 26.6 | 15.8-34.8 |
| Insulin autoantibody (nU/mL) | 2,080 | <125 | Blood Chemistry | | |
| Urinary ketone bodies | - | - | Aspartate aminotransferase (U/L) | 12 | 13-30 |
| | | | Alanine aminotransferase (U/L) | 6 | 7-23 |
| Thyroid | | | Lactate dehydrogenase (U/L) | 117 | 124-222 |
| Free thyroxine (ng/dL) | 0.87 | 0.70-1.48 | Alkaline phosphatase (U/L) | 248 | 106-322 |
| Thyroid stimulating hormone (μ IU/mL) | 1.143 | 0.35-4.940 | γ -Glutamyl transferase (U/L) | 11 | 9-32 |
| Thyrotropin receptor antibodies (IU/L) | 0.5 | <2 | Creatinine kinase (U/L) | 52 | 41-153 |
| Thyroglobulin antibodies (IU/mL) | 11 | <28 | Blood urea nitrogen (mg/dL) | 10.4 | 8.0-20.0 |
| Thyroid peroxidase antibodies (IU/mL) | 7 | <16 | Creatinine (mg/dL) | 0.54 | 0.46-0.79 |
| | | | Sodium (mEq/L) | 139 | 138-145 |
| | | | Potassium (mEq/L) | 3.3 | 3.6-4.8 |
| | | | Chloride (mEq/L) | 108 | 101-108 |

IA-2: anti-insulinoma antigen 2

was instructed to perform frequent daily blood glucose self-monitoring. However, her postprandial blood glucose levels remained in the 140-180 mg/dL range, despite nutritional therapy. The neutral protamine Hagedorn was started at 10 units before breakfast. Her insulin doses were titrated according to the fasting and postprandial blood glucose levels. Insulin aspart was added at 29 weeks' gestation. Her total insulin dose was 38 units per day at 34 weeks' gestation. She delivered a male infant, weighing 3,220 g at 40 weeks' gestation by vaginal delivery. The infant's 1- and 5-minute Apgar scores were 8 and 9, respectively.

At her six-week postpartum follow-up visit, a second 75-g OGTT was performed. The 2-hour plasma glucose level was 258 mg/dL, indicating the likelihood of overt diabetes, although her hemoglobin A1c (HbA1c) was only 5.7%, and her glycated albumin was 14.1%. A third 75-g OGTT at 4 months postpartum showed plasma glucose levels of 131 mg/dL, 356 mg/dL, and 453 mg/dL on fasting, 1-hour, and 2-hour post-glucose loads, respectively. She also had an elevated HbA1c of 6.7%, and a glycated albumin of 22.5%. Her urinary ketone bodies were negative. Based on these findings, she was diagnosed with overt diabetes and was referred to our department for further testing and treatment. She denied polydipsia, polyuria, and fatigue. After the third OGTT, she had a positive pregnancy test. Intensive insulin therapy was started, but unfortunately, she miscarried after one week. The GADA result was reported to be 57.1 U/mL at 6 months postpartum. Based on her clinical course and GADA-positive status, she was diagnosed with T1D and admitted for further work-up.

Her body mass index was 16.9 kg/m². Her physical examination was unremarkable. The laboratory data measured at admission are shown in Table 1 and indicate normal liver,

kidney, and thyroid functions. Her tests were negative for anti-thyroid antibodies, including thyrotropin receptor antibodies, anti-thyroglobulin antibodies, and anti-thyroid peroxidase antibodies. She had elevated levels of anti-insulinoma antigen 2 antibody (IA2A), which was measured at admission. An intravenous glucagon stimulation test was performed, with blood samples for glucose and C-peptide taken at baseline and at 6 minutes. Her plasma glucose levels were 75 and 103 mg/dL at baseline and 6 minutes, respectively, and the corresponding serum C-peptide levels were 0.5 and 1.2 ng/mL at baseline and at 6 minutes, respectively. The urinary C-peptide excretion was 13.3 μ g/day, which suggested that she was in an insulin-dependent state. A continuous subcutaneous insulin infusion (CSII) was started at a dose of 8 units per day. She was discharged with CSII and remained in good glycemic control. She did not exhibit signs of diabetic neuropathy, retinopathy, or nephropathy. We retrospectively measured levels of GADA and IA2A in a stored blood sample at the second 75-g OGTT. The levels of GADA and IA2A were 37.4 and 8.3 U/mL, respectively. Her clinical course is shown in Figure.

Discussion

We encountered a woman with a history of GDM who was subsequently diagnosed with T1D in the early postpartum period, based on the results of a 75-g OGTT at 4 months postpartum. In this case, her relatively young age and parity, insulin treatment during pregnancy, and pancreatic beta-cell autoantibodies positivity were the factors possibly associated with the development of T1D. Jarvela et al. reported that age younger than 30 years, insulin treatment for GDM, islet cell antibody positivity, and the presence of

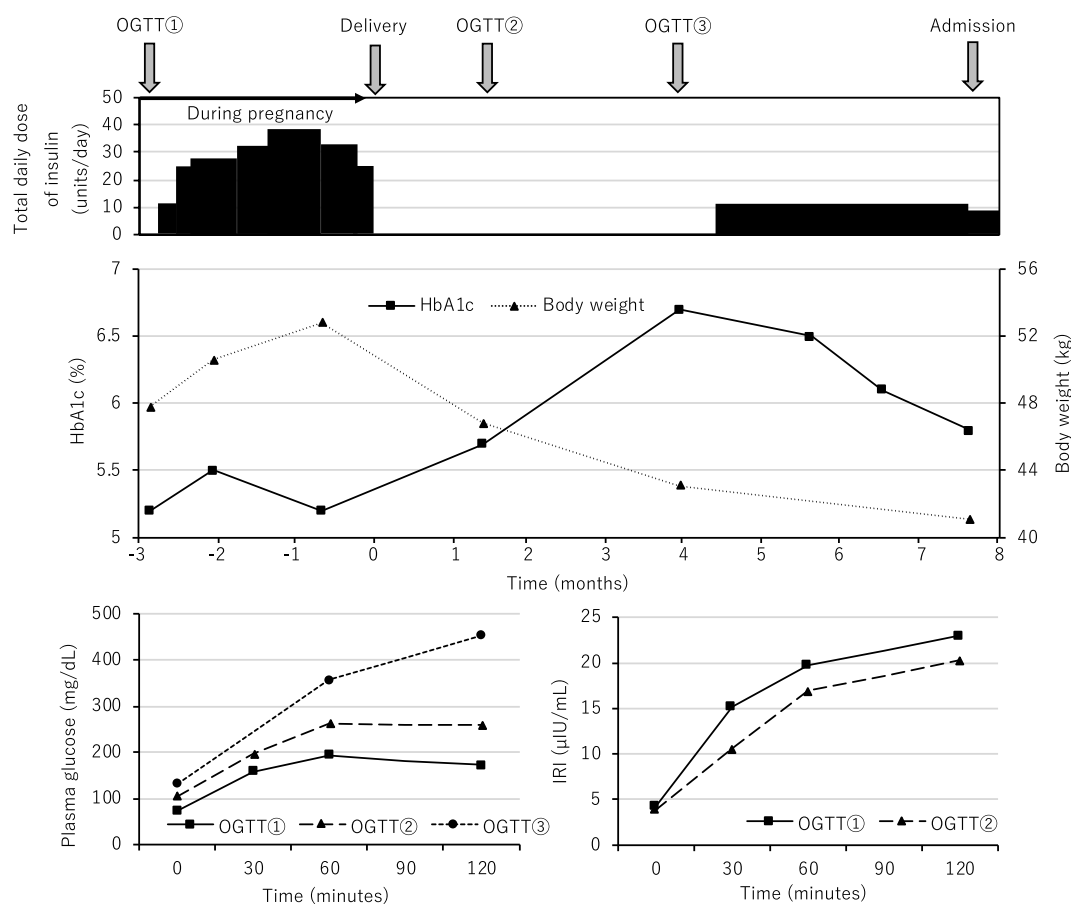


Figure. The clinical course of the patient in this case. IRI: immunoreactive insulin; OGTT: 75-g oral glucose tolerance test

GADAs were all associated with an increased risk of developing T1D (4). Our patient exhibited findings that were consistent with three of the above-mentioned characteristics. Fuchtenbusch et al. reported that the risk of developing T1D increased with the number of antibodies present at delivery (3). Our patient was positive for both GADA and IA2A, which indicates that the odds ratio for developing T1D postpartum would be at least 49.6, according to that study's findings (3). Fuchtenbusch et al. also reported that women with one or more pregnancies before the index pregnancy had a higher risk of developing T1D in the postpartum period than women after their first pregnancy (3). In this case, the patient had had one pregnancy prior to the index pregnancy. Taken together, the above characteristics indicate that our patient was predisposed to developing T1D postpartum.

A 75-g OGTT is recommended at the 4- or 6- to 12-week postpartum visit in women with a history of GDM (17-19). In this patient, the OGTT was performed at the 6-week postpartum visit. In our previous study, only 6 out of 169 (3.6%) Japanese women with GDM showed patterns consistent with diabetes at their 6- to 8-week postpartum 75-g OGTTs (20), indicating the low prevalence of diabetic patterns at 6 to 8 weeks postpartum. Lobner et al. reported that almost 50% of women with pancreatic beta-cell autoantibodies developed diabetes within 6 months of delivery, which was relatively rapid compared to those without autoantibod-

ies (21). Therefore, careful attention should be paid to the possibility of developing T1D in women with abnormal 75-g OGTTs in the early postpartum period.

Lundberg et al. reported that, compared to women who were GADA-negative, women who were GADA-positive had significantly increased 0- and 2-hour plasma glucose levels and decreased serum insulin levels at 0 and 30 minutes on the postpartum 75-g OGTT (15). In our patient, the magnitude of the rise in the 2-hour plasma glucose levels on the OGTT was greater than that of the plasma glucose levels at 0 hour on the first, second, and third OGTTs. High-intensity breastfeeding improves glucose metabolism and insulin sensitivity (22, 23). The infant in this case was primarily being breastfed around the time of the second 75-g OGTT but had transitioned to primarily formula feeding around the time of the third 75-g OGTT, which may have contributed to the deterioration of glycemic control from the second to the third OGTT. The measurement of plasma glucose levels at 2 hours on the OGTT may provide an opportunity for an early diagnosis of T1D.

Comparing the first 75-g OGTT to the second 75-g OGTT, the insulinogenic index (24, 25) decreased from 0.13 to 0.07, and the homeostasis model assessment of the beta-cell function (26) decreased from 154.8 to 34.2. In contrast, the homeostasis model assessment of insulin resistance (26) increased from 0.78 to 1.00, the Matsuda index (27) de-

Table 2. Case Reports of SPIDDM after Diagnosis of GDM.

| Case | Age | BMI (kg/m ²) | Family history | GADA | HbA1c (%) | F-CPR (ng/mL) | Insulin | Duration (months) | Reference |
|------|-----|--------------------------|----------------|------|-----------|---------------|---------|-------------------|--------------|
| 1 | 36 | 21.6 | - | + | 9.9 | 0.33 | + | 120 | (32) |
| 2 | 34 | 18.9 | + | + | 6.7 | 0.59 | + | 1 | (33) |
| 3 | 42 | 18.2 | + | + | 8.9 | 0.23 | + | 72 | (34) |
| 4 | 31 | 22.1 | + | + | 5.5 | 0.62 | + | 1 | (34) |
| 5 | 27 | 16.9 | + | + | 6.7 | 0.5 | + | 9 | present case |

SPIDDM: slowly progressive type 1 diabetes mellitus, GDM: gestational diabetes mellitus, Age: age at diagnosis of SPIDDM, BMI: non-pregnant body mass index (except for case 4 which was measured at 28 weeks' gestation), Family history: family history of diabetes mellitus, F-CPR: non-pregnant fasting serum C-peptide, GADA: anti-glutamic acid decarboxylase antibody, HbA1c: hemoglobin A1c measured at the time of SPIDDM diagnosis, Insulin: insulin treatment during pregnancy, Duration: timespan between the diagnosis of GDM and the diagnosis of SPIDDM

creased from 10.5 to 8.7, and the insulin secretion-sensitivity index-2 (ISSI-2) (28) decreased from 1.12 to 0.56. Taken together, these findings suggest that the insulin secretion, insulin sensitivity, and beta-cell function all decreased. Lundberg et al. showed that the beta-cell function, as measured by insulin secretion adjusted for insulin sensitivity, was significantly impaired when they compared women who were GADA-positive to those who were GADA-negative at three months postpartum (15). The beta-cell function assessed by the ISSI-2 for the patient in this case had decreased by 50% after only 4 months, which is indicative of the rapid destruction of beta-cells. The immunological changes associated with pregnancy may have contributed to the deterioration of her glycemic control and the development of T1D. Assessments of the beta-cell function using the 75-g OGTT postpartum might help identify patients who are GADA-positive.

A nationwide Japanese survey on the prevalence of T1D associated with pregnancy showed that 12 patients developed T1D during pregnancy or in the early postpartum period. Nine of those 12 patients developed fulminant T1D, while the remaining 3 developed acute-onset T1D (29). Our patient met the diagnostic criteria for slowly progressive T1D as published by the Japan Diabetes Society. This condition, formally termed slowly progressive insulin-dependent diabetes mellitus (SPIDDM), is based on the presence of GADA and the absence of ketosis or ketoacidosis at the onset of diabetes mellitus without the need for insulin treatment (30). Our patient did not present with ketosis or ketoacidosis in the postpartum period, although the onset was suspected to have occurred before the second postpartum OGTT. However, the possibility of acute-onset T1D (31) cannot be excluded in this patient. Based on the intravenous glucagon stimulation test results and the urinary C-peptide excretion levels, this patient was in an insulin-dependent state at time of admission. In addition, her beta-cell function, as assessed by the ISSI-2, indicated the rapid destruction of the beta-cells. If the 75-g OGTT postpartum had not been performed, the patient might have presented with diabetic ketoacidosis and shown a clinical course consistent with acute-onset T1D. As mentioned, she was diagnosed with SPIDDM rather than acute-onset T1D, based on the absence of ketosis without the requirement of insulin for at

least three months from the onset of diabetes, although GADA was positive.

We searched PubMed and the Japanese Igaku-Chuo-Zasshi database using a combination of the key words, "slowly progressive type 1 diabetes mellitus" and "gestational diabetes mellitus". The characteristics of five patients, including the present patient, were consistent with SPIDDM following a diagnosis of GDM (Table 2) (32-34). The mean age of these patients was 34 years, and the mean BMI was 19.5 kg/m², which was relatively low. This low BMI may provide clues for identifying women who are GADA-positive, since these women have been diagnosed with GDM and are known to be leaner than women who are GADA-negative with GDM (8). All five patients were prescribed insulin during pregnancy. Each patient had characteristics that predisposed them to developing T1D. Patients 1 and 3 had longer time-spans between the diagnoses of GDM and SPIDDM and higher HbA1c levels and lower serum C-peptide levels than the other patients. These two patients were insulin-dependent, according to their fasting serum C-peptide levels, possibly due to delayed insulin therapy resulting in rapid beta-cell destruction. Insulin therapy has been known to preserve the beta-cell function in patients diagnosed with SPIDDM (35). Patients 2 and 4 were diagnosed with SPIDDM shortly after the diagnosis of GDM during pregnancy. The blood glucose levels are frequently measured in women whose pregnancies are complicated by GDM. This allows for the early diagnosis of SPIDDM and prevents the further deterioration of glycemic control.

In conclusion, we encountered a patient with an early postpartum diagnosis of T1D after a pregnancy complicated by GDM. T1D can be overlooked in women diagnosed with GDM. Therefore, these patients will need not only fasting plasma glucose and HbA1c tests but also OGTTs in the postpartum period, which may be more helpful for identifying T1D than measuring only fasting plasma glucose and HbA1c. Glycemic control deteriorates more rapidly in those who have pancreatic beta-cell autoantibodies, including GADA, although the prevalence of GADA is low. Women with GDM who have clinical features suggestive of future T1D should have their GADA levels measured for the early detection of T1D.

The authors state that they have no Conflict of Interest (COI).

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