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Anti-glutamic Acid Decarboxylase Antibody-Positive Gestational Diabetes Mellitus with Autoimmune Type 1 Diabetes Mellitus in the Early Postpartum Period: A Case Report and Literature Review

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Gestational diabetes mellitus (GDM) is a state of pre-diabetic impaired glucose tolerance initially occurring during pregnancy. Although abnormalities in glucose metabolism normally resolve rapidly after delivery, women with GDM have a higher lifetime risk of developing diabetes mellitus than those without GDM; thus, postpartum healthcare is essential. Of all GDM patients, 5%-10% test positive for diabetes-related autoantibodies, which increase the risk of developing type 1 diabetes mellitus (T1DM). Autoantibody measurement in GDM screening remains debatable; however, it may be useful for the postnatal follow-up of GDM patients at high risk of developing T1DM. We treated a 29-year-old woman who was GDM positive for anti-glutamic acid decarboxylase antibody (GADA) requiring high-dose insulin therapy during pregnancy. As the patient tested positive for GADA, she received judicious postpartum management, allowing for early diagnosis of T1DM and resumption of treatment. Her insulin secretory capacity was preserved at 1 year after parturition, suggesting either slowly progressive insulin-dependent T1DM or latent autoimmune diabetes in adults. This was a rare case of slowly progressive insulin-dependent T1DM or latent autoimmune diabetes in adults in the early postpartum period, but the fact that GADA was positive during pregnancy enabled early treatment without overlooking it. Measuring diabetes-related autoantibodies in patients considered to be at a high risk for T1DM, such as those who are of slim build, young, or suffering from autoimmune thyroid disorders, may be important for appropriate individualized follow-up.

Keywords: anti-glutamic acid decarboxylase antibody (anti-GADA); gestational diabetes mellitus (GDM); latent autoimmune diabetes in adults (LADA); slowly progressive insulin-dependent type 1 DM (SPIDDM)
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Introduction

Gestational diabetes mellitus (GDM) is defined as a state of pre-diabetic impaired glucose tolerance identified or occurring for the first time during pregnancy, but it does not include overt diabetes during pregnancy or before GDM (American Diabetes Association 2013; Araki et al. 2020) (Table 1). It is a common complication of pregnancy, occurring in 2%-17% of pregnant women (Corrado et al. 2006; Buchanan et al. 2007; Hunt and Schuller 2007). In most cases, abnormalities in glucose metabolism rapidly resolve after delivery. However, the recurrence rate in the succeeding pregnancy is high at 34%-48% (England et al. 2015). Eventually, 5.7% of women with GDM develop type 1 diabetes mellitus (T1DM), whereas approximately 50% develop type 2 diabetes mellitus (T2DM) postpartum (Auvinen et al. 2020). This indicates that managing GDM solely during pregnancy is insufficient. In addition to the previously recommended 75 g oral glucose tolerance test (OGTT) at 6-12 postpartum weeks, the Guideline for Obstetrical Practice in Japan (2020) now includes the recommendation to conduct subsequent postpartum monitoring for patients diagnosed with GDM (https://www.jsog.or.jp/activity/pdf/gl_sanka_2020.pdf). Conversely, in clinical practice, if a 75-g OGTT at 6-12 postpartum weeks reveals no abnormalities, regular monitoring is often terminated.

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Table 1. Diagnostic criteria for gestational diabetes mellitus, overt diabetes in pregnancy, and pre-gestational diabetes mellitus.

Diagnostic criteria	Level
Gestational diabetes mellitus	
Fasting plasma glucose value	≥ 92 mg/dL (5.1 mmol/L)
1 h post-OGTT plasma glucose value	≥ 180 mg/dL (10.0 mmol/L)
2 h post-OGTT plasma glucose value	≥ 153 mg/dL (8.5 mmol/L)
Overt diabetes in pregnancy	
① Fasting plasma glucose	≥ 126 mg/dL (7.0 mmol/L)
② HbA1c	≥ 6.5% (48 mmol/moL)
Women with casual/post-OGTT blood glucose ≥ 200 mg/dL (11.1 mmol/L) should be examined to see if they meet ① or ② above, with the potential diagnosis of overt diabetes in pregnancy in mind.	
Pre-gestational diabetes mellitus	
Diabetes already diagnosed before pregnancy	
Pregnancy associated with unequivocal evidence of diabetic retinopathy	

OGTT, oral glucose tolerance test. Adapted from Araki et al. (2020) Japanese Clinical Practice Guideline for Diabetes 2019.

Long-term follow-up of all GDM cases is difficult in practice. To properly manage GDM cases after delivery, it is necessary to select high-risk cases from the course of pregnancy and focus on diabetes-related autoantibodies. Around 5%-10% of patients with GDM reportedly test positive for these autoantibodies (Lapolla et al. 2009). Autoimmune GDM women are known to be at high risk of developing T1DM, with an increased risk of requiring insulin treatment at a comparatively early stage in the postpartum period (Incani et al. 2019).

In this case, we treated a patient diagnosed with GDM who tested positive for anti-glutamic acid decarboxylase antibody (GADA) and was administered insulin for T1DM at two months postpartum. This case is classified as slowly progressive insulin-dependent type 1 diabetes mellitus (SPIDDM) or latent autoimmune diabetes in adults (LADA), as the patient maintained her insulin secretory capacity and was positive for autoantibodies. There are very few reports of developing SPIDDM/LADA triggered by pregnancy (Wucher et al. 2011; Ichimura et al. 2017; Ohigashi et al. 2019); thus, this case is relatively rare. In view of this experience, we consulted the literature on pregnancy outcomes and postpartum courses of autoantibody-positive and -negative women with GDM, with the aim of identifying better methods of postnatal management of GDM patients.

Case Presentation

The patient was a 29-year-old woman (G1P0) with a pre-pregnancy body mass index (BMI) of 19.1 kg/m^2 (height: 155 cm, weight: 46 kg) and with no family history of thyroid disease and diabetes mellitus. The patient was neither a drinker nor a smoker. She displayed no glucose tolerance impairment prior to pregnancy. She was diagnosed with Graves' disease since the age of 26 years. Owing to her intake of propylthiouracil, she had developed liver function impairment, rashes, and granulocytopenia. Consequently, the patient is currently being treated with 5 mg of methimazole every other day.

History of current disease

The patient naturally conceived, and her pregnancy was managed at our hospital from the first trimester onwards. As the patient's Graves' disease had not entered remission, methimazole treatment could not be withdrawn and had to be continued after her pregnancy was confirmed, and thyroid function was well-controlled during the pregnancy. Thyroid-stimulating hormone receptor autoantibody level was positive but at levels not considered to increase the risk of causing neonatal Graves' disease (5.8 IU/L at 15 weeks' gestation and 3.9 IU/L at 20 weeks' gestation) (Alexander et al. 2017).

At 10 weeks 2 days gestation, casual blood glucose was normal at 79 mg/dL. At 27 weeks 1 day gestation, a 50-g glucose challenge test showed abnormal results of 339 mg/dL. Further testing at 27 weeks 4 days gestation revealed a fasting blood glucose level of 120 mg/dL and hemoglobin A1c (HbA1c) at 6.4%. Although the patient did not meet the criteria for overt diabetes in pregnancy (Table 1), a glucose challenge was considered dangerous and was not conducted. She was referred to our hospital's Department of Metabolism and Endocrinology on the same day and began self-monitoring of blood glucose (SMBG). At 28 weeks 1 day gestation, the patient was examined for diabetic retinopathy, which was not observed. Therefore, she was diagnosed with GDM (Table 1). Postprandial blood glucose was high, in the 200-400 mg/dL range (reference range < 120 mg/dL), and the patient was subsequently started on insulin therapy [insulin aspart (3-3-3 units) and insulin detemir (0-0-0-3 units)].

At 29 weeks 1 day gestation, the patient was admitted to the hospital for blood glucose control. She was placed

on a 1,840-kcal diet for dietary management. Blood glucose levels on admission were 68 mg/dL before lunch, 174 mg/dL after lunch, 120 mg/dL before supper, and 264 mg/dL after supper, demonstrating high postprandial blood glucose. HbA1c on admission was 6.9%, and GADA on admission was 1,210 U/mL (reference range < 5 U/mL). Fasting serum C-peptide (s-CPR) was 1.19 ng/mL (reference range ≥ 0.6 ng/dL) and daily urinary C-peptide (U-CPR) was 120.6 μg/day (reference range > 20 μg/day), which were both within normal limits, indicating that insulin secretion was maintained. At 30 weeks 4 days gestation, continuous glucose monitoring was initiated. Insulin was gradually increased, with the doses of insulin aspart and insulin detemir being increased to 24-8-19 units and 3-0-0-0 units, respectively.

At 31 weeks 3 days gestation, the patient was discharged. Blood glucose at discharge had improved to 76 mg/dL before breakfast, 177 mg/dL after breakfast, 106 mg/dL before lunch, 134 mg/dL after lunch, 76 mg/dL before supper, and 115 mg/dL after supper. After discharge, blood glucose levels remained within control, and the insulin dosage was maintained until delivery. The amniotic fluid volume and estimated fetal weight remained within normal range throughout the pregnancy.

At 37 weeks 6 days gestation, she was hospitalized due to the onset of labor pains. At 38 weeks 0 days gestation, the patient delivered naturally. The infant was a male weighing 2,933 g, with Apgar scores of 8 and 9 at 1 and 5 min, respectively. The infant's umbilical aortic blood pH was 7.32. Postpartum, blood glucose was measured before and after every meal, and treatment was provided on a sliding scale of insulin therapy.

On the day of delivery, high blood glucose levels were observed, with a fasting blood glucose 167-222 mg/dL and postprandial blood glucose 213-223 mg/dL, but these improved in the succeeding days. On the fourth postpartum day, glucose levels were generally stable at 83-107 mg/dL before meals and 117-146 mg/dL after meals; consequently, insulin therapy was discontinued before the patient was discharged. SMBG was continued after discharge.

One month after delivery, fasting blood glucose (80 mg/dL) and glycated albumin (13.3%; reference range 11-16%) were found to be within normal levels, and no exacerbation was observed.

On the 58th postpartum day, postprandial blood glucose increased to ≥ 200 mg/dL; thus, T1DM was diagnosed. As s-CPR was high at 2.87 ng/mL, the insulin secretory capacity was assumed to be preserved, but insulin aspart (0-2-2 units) was restarted to protect pancreatic function. The insulin dose was gradually increased, and insulin lispro (4-5-6 units) and insulin detemir (0-0-0-2 units) were still administered at 19 postpartum months. Additionally, at 19 postpartum months, s-CPR was low at 0.59 ng/mL; hence, the insulin secretory ability was considered to be reduced. Thyroid function was well controlled by methimazole, without further incidents of postpartum thyroiditis. Fig. 1 presents a diagram illustrating the therapeutic course of treatment during pregnancy and after delivery.

Infant's course

Because the baby was born from a mother with GDM, there was a considerable risk of hypoglycemia in the newborn; hence, the neonate was placed in an incubator and carefully observed. His blood glucose was regularly checked, and his blood oxygen saturation levels were monitored. From day one, he exhibited poor sucking and frequent apneic episodes and was therefore admitted to the neonatal intensive care unit (NICU). Hypoglycemia was not observed. Abdominal radiography and cardiac, intracranial, and abdominal ultrasound scans revealed no abnormalities, and blood test results were also unremarkable.

After NICU admission, the neonate's respiratory status gradually improved, but periodic breathing with short pauses occurred until day 15. The results of thyroid function tests conducted on days 1 and 5 were normal.

He was discharged on day 20 (corrected gestational age 40 weeks 6 days) weighing 3.1 kg.

Informed consent and ethics approval

Written informed consent was obtained from the patient. This study was approved by the ethics board of Akita University Graduate School of Medicine and Faculty of Medicine (approval number: 2899).

Discussion

In this study, we report the case of a patient with GDM who tested positive for GADA. She was considered to be at a high risk due to high GADA levels and was vigilantly managed after delivery, resulting in early diagnosis and early intervention.

Performing risk assessment based on prenatal test results and patient's clinical course is necessary for postpartum management. A high BMI, a family history of diabetes, and advanced maternal age are reportedly associated with the future risk of T2DM (Rayanagoudar et al. 2016); nevertheless, only few Japanese studies have reported on the measurement of GADA and other diabetes-related autoantibodies, which are risk factors for T1DM.

Although the reported autoantibody positivity rate in GDM varies in different studies, it is generally believed to be in the range of 5%-10% (Lapolla et al. 2009). The types of autoantibodies involved are islet cell autoantibodies, insulin autoantibodies, tyrosine phosphatase-like islet antigen autoantibody, zinc transporter 8 autoantibody, and GADA. Of these, GADA is the most widely reported, with an incidence of 0%-10.8% in GDM (Unnikrishnan et al. 2016). In Japan, only one report on GADA exists: a single-center study which reported an incidence rate of 3.5% (Ikenoue et al. 2019). Furthermore, one study found that 50% of women with autoimmune GDM went on to develop T1DM (Nilsson et al. 2007), suggesting that they are at high risk during pregnancy and the postpartum period. It

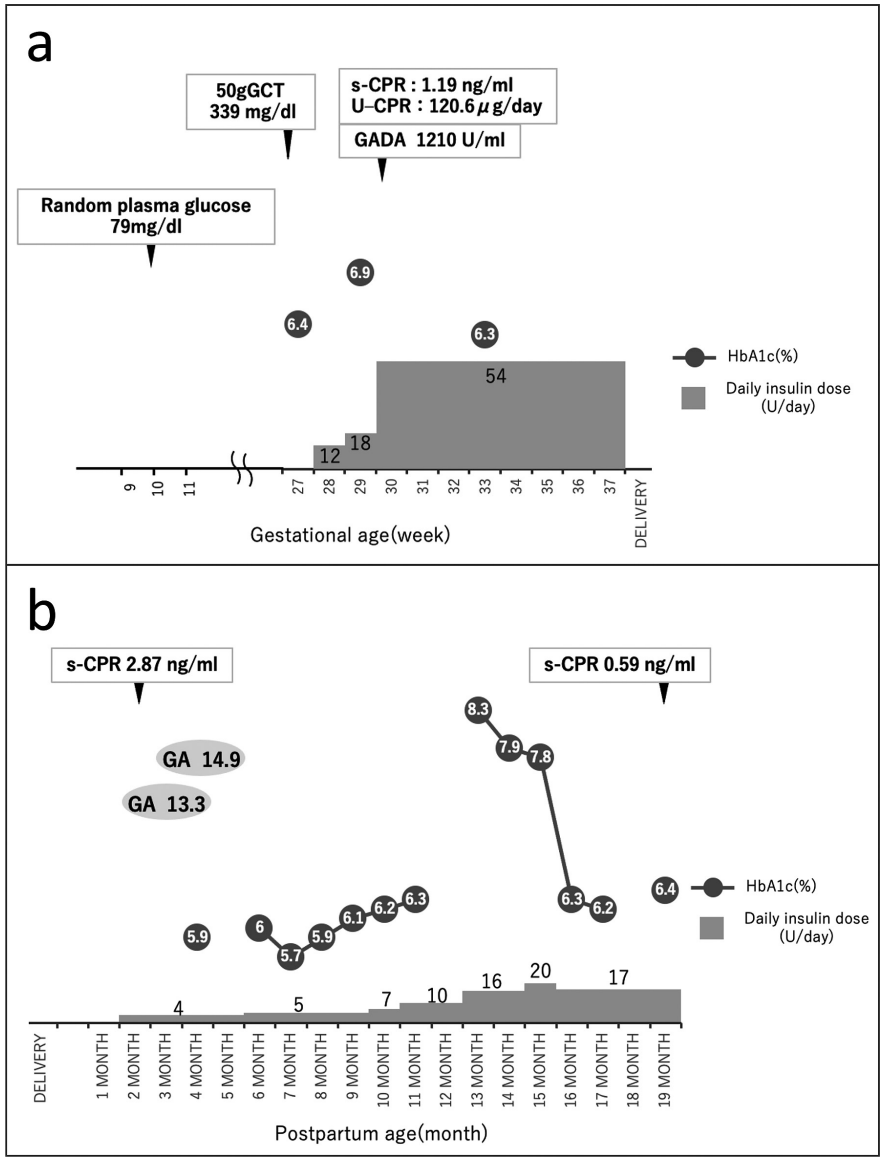

Fig. 1. Clinical course of this case during pregnancy and after delivery.
(a) Clinical course during pregnancy. No abnormalities in the blood glucose level were found in the first trimester of pregnancy. Gestational diabetes was diagnosed at 27 weeks of gestation, at which point a high dose of insulin was required. The patient delivered spontaneously at 38 weeks and 0 days. (b) Clinical course after delivery. After delivery, the blood glucose level improved, and it was possible to discontinue insulin treatment. However, hyperglycemia gradually began to be observed. At 2 months after delivery, she was diagnosed with type 1 diabetes mellitus, and insulin treatment was resumed.
GCT, glucose challenge test; s-CPR, fasting serum C-peptide (reference range ≥ 0.6 ng/dL); U-CPR, daily urinary C-peptide (reference range > 20 μg/day); GADA, anti-glutamic acid decarboxylase antibody (reference range < 5 U/mL); GA, glycated albumin (%) (reference range 11-16%).

has also been reported that the progression of GDM to T1DM occurs faster than the progression to T2DM (mean time to development of diabetes postpartum = 1.9 ± 1.0 vs. 5.9 ± 4.8 years) (Unnikrishnan et al. 2016); therefore, women with autoimmune GDM must be thoroughly followed up at postpartum to enable an early diagnosis and prevent presentation in acute hyperglycemic crises.

The Japan Diabetes Society (JDS) classifies type 1 diabetes mellitus as fulminant, acute onset, or SPIDDM based upon clinical presentation and progression (Araki et al. 2020). SPIDDM is defined only in Japan and does not exist as a category internationally but is considered equivalent to the concept of LADA (Rajkumar and Levine 2022). Although the exact definition of LADA is still under debate and no clear diagnostic guidelines are currently available, it is considered to be a form intermediate between type 1 and type 2 diabetes mellitus (Pieralice and Pozzilli 2018) (Table 2). Otherwise, the initial course of LADA/SPIDDM is similar to that of T2DM; however, their management differs. Early initiation of insulin therapy has been shown to be an

Table 2. Clinical, biochemical, and pathogenetic features of T1DM, T2DM, and latent autoimmune diabetes in adults (LADA).

	T1DM	LADA	T2DM
Clinical features			
Age at onset	Childhood/ adolescence	30-50 years	Adulthood
Symptoms of hyperglycemia at onset	Frequency acute	Subclinical (rarely acute)	Silent/subclinical
Insulin requirement	At diagnosis	> 6 months after diagnosis	Absent or years after diagnosis
Insulin resistance	No change	Increased/no change	Increased
BMI (kg/m^2)	< 25 (frequency < 18)	< 25 (rarely > 25)	> 25
History of autoimmune disease	Positive	Positive	Negative (no correlation)
Biochemical features			
Islet-cell autoantibodies	High titer (rarely low)	High/low titer	Absent
C-peptide levels at diagnosis	Non-detectable (rarely decreased)	Decreased but still detectable	Normal/increased
Pathophysiology features			
Family history of diabetes	Negative/positive	Negative/positive	Frequency positive
Family history of autoimmune disease	Frequency positive	Frequency positive	Negative (no correlation)

BMI, body mass index. Based on Pieralice and Pozzilli (2018).

Table 3. Case reports of pregnancy-related slowly progressive insulin-dependent type 1 diabetes mellitus (SPIDDM).

Case	Age	BMI (kg/m^2)	GADA (U/ml)	Autoimmune disease	Reference
1	38	16.7	22,600	Graves' disease	Terashima et al. (2002)
2	25	30.8	1,069	Hashimoto's thyroiditis	Miyamoto et al. (2011)
3	34	18.9	5.1	No	Ide et al. (2011)
4	29	30.3	10.3	Not clear	Kiyotoki et al. (2016)
5	36	18.2	20	Not clear	Ichimura et al. (2017)
6	31	22.1	30	Hashimoto's thyroiditis	
7	23	20.1	10	Not clear	Morita et al. (2017)
8	27	16.9	57.1	No autoimmune thyroid disease	Ikeoka et al. (2018)
9	40	26.6	5,530	Idiopathic thrombocytopenic purpura	Suzuki et al. (2019)
10	35	19.8	2.7	Hashimoto's thyroiditis	
11	34	20.1	281	No	
12	37	35.9	250	No	
13	30	27.3	≥ 2,000	Hashimoto's thyroiditis	Ohigashi et al. (2019)
14	29	19.1	1,210	Graves' disease	Present case

BMI, body mass index; GADA, glutamic acid decarboxylase antibody (reference range < 5 U/mL).

effective and safe method of treatment for LADA (Thunander et al. 2011; Pieralice and Pozzilli 2018).

The fasting hypoglycemia observed in this case during the early postpartum period is thought to be attributable to the delay in postprandial insulin secretion and excessive insulin secretion, and this condition is often observed in T2DM. The patient exhibited initial symptoms similar to those of T2DM but was GADA-positive with preserved insulin secretory function. Hence, the patient's case was classified as SPIDDM. Insulin therapy was initiated early after diagnosis; however, the amount of insulin was gradually increased. At this time, the patient was not insulin-dependent but could become so if her condition had progressed. In our hospital, we examine for GADA, which is the most common; if negative, we subsequently search for other islet-associated autoantibodies and HLA. Therefore, no searches other than for GADA were performed in this case.

Determining GADA positivity or negativity is very useful for postpartum management. Nonetheless, there exists little evidence to support the universal screening of women with GDM (Incani et al. 2019). Selecting a group with a high risk of becoming GADA-positive (i.e., a high risk of developing T1DM in the future) is more optimal. Identified risk factors for autoimmune GDM include young age (Takeda et al. 2002; Incani et al. 2019), normal body

weight (Ikenoue et al. 2019), insulin treatment for GDM (Takeda et al. 2002), and complications of autoimmune thyroid disease (Järvelä et al. 2006), and the patient described in our report met these criteria. We searched PubMed and ICHUSHI for articles on pregnancy-related SPIDDM that were published from 2002 until the present. As a result, we identified 9 reports and 13 cases (Terashima et al. 2002; Miyamoto et al. 2011; Ide et al. 2011; Kiyotoki et al. 2016; Ichimura et al. 2017; Morita et al. 2017; Ikeoka et al. 2018; Suzuki et al. 2019; Ohigashi et al. 2019). A review of the clinical course of 14 patients, including this patient, revealed that patients with a BMI < 25 kg/m^2 (9 cases), patients below 35 years of age (9 cases), and comorbidities with autoimmune thyroid disease (10 cases) were relatively common (Table 3). This result supports that of a previous report.

In the current clinical practice for GDM, the selection of high-risk cases and the measurement of GADA can enable appropriate GDM management and may improve the postpartum and lifelong health of women.

In conclusion, we encountered a rare case of SPIDDM/LADA in the early postpartum period. Since our patient was anti-GADA-positive during pregnancy, this prompted us to administer appropriate postpartum care and intervention. Insulin resistance increases during pregnancy, offering a good opportunity for the early detection of the risk of developing diabetes mellitus in the future. Improving the postpartum monitoring of GDM patients may lead directly to improved healthcare for women.

We suggest that testing for diabetes-related autoantibodies, including GADA, to determine the appropriate postpartum monitoring should be required for patients with low BMI, those who are young, or those suffering from autoimmune thyroid disorders, as they are considered to be at a high risk for LADA development.

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Author Contributions

A.F., Y.O., M.K., and H.M. were the treating obstetricians. A.F. carried out the retrospective review of the case, and participated in the design, writing, and organization of the manuscript. Y.T. conceived the study and its design. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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