Fulminant Diabetes Mellitus Associated with Pregnancy: Case Reports and Literature Review

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Abstract. We report two cases of type 1 diabetes mellitus fulminantly developed as diabetic ketoacidosis (DKA) at 19 weeks of gestation and immediately after delivery. Development of type 1 diabetes around pregnancy is not rare, but its fulminant development is highly uncommon. We also review the relevant literature concerning mostly Japanese cases. In our cases, the group of patients with fulminant progressive diabetes mellitus associated with pregnancy required insulin replacement therapy even after the acute period and showed high value of pancreatic exocrine enzymes, i.e. amylase, elastase, and lipase. The phenotype of this group was similar to “nonautoimmune, fulminant type 1 diabetes” described by Imagawa *et al.*, where the laboratory data of type 1 diabetes-related autoantibodies showed negative. It is well known that autoimmune diseases are in good control during pregnancy. Our present finding suggests that this type of fulminant type 1 diabetes mellitus associated with pregnancy might develop as a consequence of a nonautoimmune mechanism.

Key words: Type 1 diabetes, Pregnancy, Diabetic ketoacidosis

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WE encountered two cases of type 1 diabetes mellitus fulminantly developed as diabetic ketoacidosis (DKA) associated with pregnancy. Although development of type 1 diabetes during pregnancy is not uncommon, it seldom develops fulminantly as DKA [1]. The clinical course of this patient is presented together with a review of the relevant literature and a discussion of the mechanism.

Case Report

Case 1

A 37-year-old Japanese woman, gravida 2, para 1,

was admitted at 19 weeks gestation with nausea, abdominal fullness, and excessive thirst, which developed the day before examination. The course of pregnancy had been uneventful up to this point. Previously she had delivered a girl after a normal, full term pregnancy 5 years prior to this admission. During that pregnancy, urinary sugar had always been negative. She had been infertile since then and the current pregnancy was brought about by the *in vitro* fertilization and embryo transfer therapy and the fetus were gemini. A regular examination at 15 weeks gestation was normal, and no glycosuria was presented in the monthly urine tests. Family history was negative for diabetes.

On physical examination, she was alert, body temperature 36.8°C, pulse 111/min regular, respiration 20/min, and blood pressure 117/62 mmHg. Her height was 158 cm, body weight 49 kg, body mass index 19.6 kg/m². Skin and tongue were dry and the abdomen was normally protruded for the gestational

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stage.

Random sample plasma glucose was 31 mmol/l, with 3+ urinary ketone bodies. Arterial pH was 7.13, bicarbonate 4.6 mmol/l, plasma β -hydroxybutyrate 6,860 μ mol/l, and lactic acid 1.1 mmol/l. Despite unequivocal presence of DKA, HbA1c was within the normal range, 5.7%. In addition, leukocytosis, and elevation of serum pancreatic enzymes such as amylase, elastase, and lipase, and C-reactive protein were found. Urinary C-peptide excretion was extremely low (3.3 μ g/day) on the following day. Antibody against glutamic acid decarboxylase (α GAD ab) was negative but anti-insulin antibody was trace positive in the sera obtained before administration of insulin. Anti-insulin antibody was determined by the polyethyleneglycol method. To this end, tracer amount of 125 I-labeled insulin was added to the patient's serum and immunoglobulins were precipitated by polyethyleneglycol. There was no increase in the titer of antibodies against coxsackie B1, B2, B3, B4, B5, B6, A9 viruses in the pair serum. HLA typing was A2, A24, B54, B62, CW1, CW3, and DR4. In Japanese patients with type 1 diabetes, increased frequency of A24, B54, CW1, DR4 and [DR4+DR9] and decreased frequency of B52 and DR2 are established [2].

Diagnosis of DKA was made, treatment with fluid and *iv* insulin was immediately initiated, and satisfactory recovery from DKA ensued. By the morning of the 2nd hospitalization day, plasma glucose was gradually lowered to 11 mmol/l, without episode of hypoglycemia, arterial pH returned to 7.34 without administration of bicarbonate, and the symptoms were resolved. However, on the 3rd hospitalization day, she gave stillbirth. The pancreas appeared normal on the abdominal CT-scan performed on the 16th hospital day.

She did not experience a so-called honeymoon period [3] and has continuously required multiple daily insulin injection (0.6–0.8 U/kg/day) since then, to maintain HbA1c < 8.5%. Approximately 1 year after the event, at the time of this report, insulin dose is 0.76 U/kg/day (38 U/day), random sample plasma glucose 9–20 mmol/l, HbA1c 5.8–7.7%, and urinary C-peptide < 0.5 ng/ml. There is no clinical evidence of diabetic retinopathy, neuropathy or nephropathy. Currently, α GAD ab is negative, and anti-insulin ab is still positive. However, interpretation of the current data on insulin antibody is difficult because it

may well be due to insulin injection, and not insulin autoantibody.

Case 2

A 36-year-old Japanese woman, gravida 2, para 2, who delivered a 1100 g live premature infant without any trouble at 28 weeks gestation, was admitted the day after delivery. During pregnancy, urinary sugar had been negative at 23 weeks gestation and changed to positive one week before admission. The next day after labor, she could not eat anything and felt thirsty with polyurea. After that, dyspnea occurred with clouding of consciousness, hence she was admitted to our hospital.

Random sample plasma glucose was 36.1 mmol/l, with 3+ urinary ketone bodies. Arterial pH was 7.122, bicarbonate 2.2 mmol/l, and plasma β -hydroxybutyrate 2,546 μ mol/l. Despite unequivocal presence of DKA, HbA1c was within normal range, 6.0%. In addition, leukocytosis, and elevation of serum pancreatic enzymes such as amylase, and C-reactive protein were found. Urinary C-peptide excretion was extremely low (17.7 μ g/day) on the 5th hospital day. α GAD, islet cell antibody (ICA), and insulin autoantibody were negative. Thyroid test and microsome test were also negative. HLA typing was A2, A24, B48, B54, CW1, DR4, DQ3 and DQ4.

Discussion

Pregnancy is associated with insulin resistance such that diabetes newly diagnosed during pregnancy can be the deterioration of a pre-existing mild form of asymptomatic diabetes. However, in the patients described here, we considered diabetes newly developed as DKA because urinary sugar had continuously been negative before the current admission, and HbA1c at the onset was within the normal range. Moreover, in our cases, the symptoms attributable to hyperglycemia developed just 1 day and 7 days prior to recognition of DKA. Thus, we used the term "fulminant". It is also reported that most patients who develop insulin dependent diabetes mellitus during pregnancy have type 1 diabetes [1]. The ratio of type 1 diabetes mellitus to type 2 is much higher in Europe and America than in Japan.

We experienced two cases of type 1 diabetes melli-

tus fulminantly developed as diabetic ketoacidosis associated with pregnancy. We review the relevant literature mostly with Japanese cases. In the literature, we could identify 36 patients (including our cases) who were previously glucose tolerant and then developed diabetes as DKA during pregnancy [4–10, 14]. In 6 of them, individual data were not presented [4]. Therefore, the data from 30 patients are summarized in Table 1. Salient features of these cases can be summarized as follows. First, diabetes developed so rapidly that HbA1c (or HbA1 in earlier reports) was normal in 8 (47%) out of 17 cases. In the rest ($n=13$), HbA1c was not determined, but it was noticed that the duration of hyperglycemic symptoms prior to admission was short in the majority, i.e., less than a week. Second, among 12 patients whose follow-up statuses are described, 11 (92%) patients required permanent insulin therapy, indicating that β cell failure is fully established at onset without a “honeymoon period” [3]. Third, laboratory data suggestive of pancreatitis were present in 8 out of 8 in whom serum amylase was measured. Fourth, type 1 diabetes-related autoantibodies, determined in 11 out of the 30 patients, were negative except in 2: one was definitely positive [5] and the other, the current first case, was trace positive. HLA typing was done in 9, and presence of type 1 diabetes-related HLA types was documented in 6.

This group of patients with fulminant progressive diabetes mellitus associated with pregnancy required insulin replacement therapy even after the acute period and showed high value of pancreatic exocrine enzymes, i.e. amylase, elastase, and lipase. The phenotype of this group of patients is similar to “non-autoimmune, fulminant type 1 diabetes” described by Imagawa *et al.* [11]. In this subtype, hyperglycemic symptoms developed 4.0 ± 1.7 days prior to diagnosis of DKA, the mean HbA1c value at onset was 6.4%, remission (“honeymoon”) did not occur, symptoms and laboratory data suggestive of pancreatitis were often present, and evidence for autoimmune attack of the islet β cells was absent.

It is well known that autoimmune diseases are in good control during pregnancy. Possible immunosuppression during pregnancy was proposed by Amino *et al.* [12] in relation to autoimmune thyroid disorders. Pregnancy also improves the symptoms of rheumatoid arthritis, and the disease tends to relapse within six months postpartum [13]. But, pregnancy has been recognized as a precipitating factor for developing type 1 diabetes [1]. In fact, type 1 diabetes-related autoantibodies were negative in almost all of these cases. This fact suggests that type 1 diabetes mellitus associated with pregnancy occurs because of a nonautoimmune mechanism.

Table 1. Summary of clinical data in patients with ketosis-onset diabetes during pregnancy.

	Previous Cases	Current Cases
<i>n</i>	28 ^{a)}	2
Age (yrs)	$27.4 \pm 4.5^b)$	$36.5 \pm 0.7^b)$
Gestational week	$30.9 \pm 6.0^c)$	$23.5 \pm 6.4^d)$
Duration of hyperglycemic symptoms before onset (days)	5.0 ± 5.0	4.5 ± 3.5
Plasma glucose (mmol/l)	48.7 ± 21.6	33.4 ± 3.69
Arterial pH	7.07 ± 0.16	7.12 ± 0.01
HbA1c (%)	7.7 ± 3.0 (median 6.5)	5.9 ± 0.2
Autoimmune markers (+/–)	1/8	1/1
Type 1 diabetes-related HLA (+/–)	4/3	2/0
Clinical remission (+/–)	1/9	0/2
Elevation of pancreatic enzyme (+/–)	6/0	2/0

^{a)} Three patients were reported in English literature [5, 6], 7 patients were reported in 5 Japanese case reports with English abstracts [7–10, 14], and 18 cases were reported in Japanese case reports or abstracts written in Japanese without English abstracts.

^{b)} Values are mean $\pm$ SD in Previous Cases and mean $\pm$ range in Current Cases. ^{c)} Three cases are postpartum. ^{d)} One case is postpartum.

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