Fulminant Type 1 Diabetes Mellitus Leading to Fetal Loss in a Pregnant Chinese Woman

Mei Yueh Lee,[1] Kun-Der Lin,[1,2] Yu-Hung Chang,[1,2] Ming-Chia Hsieh,[1,2,3] Pi-Jung Hsiao,[1,2] and Shyi-Jang Shin[1,2,3]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Medical University Hospital; [2]Graduate Institute of Medicine, and [3]Graduate Institute of Medical Genetics, Kaohsiung Medical University, Kaohsiung, Taiwan.

We describe a case of diabetic ketoacidosis that lead to fetal loss during week 33 of gestation in a woman who had normal glucose tolerance 11 days previously. We believe this represents a case of fulminant type 1 diabetes.

Key Words: diabetic ketoacidosis, fulminant type 1 diabetes mellitus, intrauterine fetal death
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Fulminant type 1 diabetes has been defined as a new subtype of type 1 diabetes in which pancreatic islet cell failure rapidly leads to hyperglycemia and ketoacidosis, with an average onset of 4 days. It is characterized by normal or near normal glycosylated hemoglobin levels, an absence of autoantibodies against islet cells, glutamic acid decarboxylase, insulinoma-associated protein 2/islet cell antigen 512 and insulin, as well as the involvement of the exocrine pancreas, with elevated serum levels of pancreatic enzymes [1–3]. This disease sometimes occurs during the third trimester of pregnancy or just after delivery [4], with an extremely poor prognosis for the fetus.

Case Presentation

A previously healthy 28-year-old Chinese woman presented at her local obstetrics and gynecology hospital in week 33 of gestation with generalized abdominal cramping and massive vaginal bleeding. A vaginal examination demonstrated that her cervix was fully dilated and a stillbirth was delivered approximately 12 minutes after she arrived at the hospital. The patient also complained of polyuria, polydipsia, nausea, vomiting, poor appetite, constipation and shortness of breath for 1 week before the admission, without other signs of infection. She was gravida 2 para 1, and her past medical and obstetrical histories were unremarkable. Her past obstetrical history included one prior pregnancy with the delivery of a healthy boy by normal spontaneous delivery. During that pregnancy, routine screening for gestational diabetes was negative.

During week 30 of pregnancy, the patient underwent a 50-g oral glucose tolerance test, which was mildly elevated (Table 1). A follow up 100-g oral glucose tolerance test was performed during week 31, 11 days before the present admission, and was normal (Table 1). The patient's medical records showed that urinalysis and fetal heart monitoring had been performed on multiple occasions before admission, including the day before presentation, but ketonuria and glucosuria were not found and the fetal heart rate was consistently within the normal limits.

Upon arrival at our center, physical examination revealed that the patient was alert and orientated, but

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Address correspondence and reprint requests to: Dr Kun-Der Lin, Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tzyou 1st Road, San Ming Area, Kaohsiung 807, Taiwan.
E-mail: 890073@kmuh.org.tw

Table 1. Prenatal screening report for gestational diabetes

	Value (mmol/L)	Normal range (mmol/L)
Gestational week 30/40: 50-g OGTT		
1 hr	8.11	<7.77
Gestational week 31/40: 100-g OGTT		
Fasting glucose	4.33	<5.27
1 hr	9.05	<10.00
2 hr	7.00	<8.61
3 hr	6.22	<7.77

OGTT = oral glucose tolerance test.

weak and distressed. Her vital signs were as follows: blood pressure 116/80 mmHg, pulse 142 beats/min, respiratory rate 28 breaths/min and body temperature 37.7°C. Her abdomen was not tender, and there were no localized signs of infection. Initial laboratory investigations demonstrated severe glucosuria and ketonuria, and severe metabolic acidosis (pH 7.09) with an elevated anion gap of 22 mmol/L. Hyperglycemia with leukocytosis, and a low serum sodium level, were also noticed (Table 2). Based on these findings, diabetic ketoacidosis was suspected. Further investigations for newly diagnosed diabetes mellitus, including autoimmune status, were performed, but yielded no significant results (Table 3). In the immediate postpartum period, aggressive management of diabetic ketoacidosis was conducted according to local guidelines. The patient regained good glycemic control and was discharged and treated with insulin and an oral hypoglycemic agent.

Discussion

In rare instances, diabetes mellitus may first manifest as diabetic ketoacidosis during pregnancy. In this case report, the patient was negative for gestational diabetes only 11 days before presenting with ketoacidosis. Her medical records showed that the glucose load was administered correctly and there was no mention of any emesis during the test period.

The initial mildly elevated glycosylated hemoglobin level showed that the patient did not have any significant disturbances in glucose metabolism during the months prior to this episode. Thus, this may represent

Table 2. Laboratory data upon presentation to the emergency room

	Value	Normal range
Arterial blood gas analysis on air		
pH	7.1	7.4–7.5
pCO_2 (kPa)	1.8	4.3–6.0
pO_2 (kPa)	14.8	9.6–13.8
HCO_3 (mmol/L)	4.1	22.0–30.0
Blood/plasma chemistry		
Serum fasting glucose (mmol/L)	34.2	4.2–6.1
Sodium (mmol/L)	124.0	136.0–146.0
Potassium (mmol/L)	5.4	3.5–5.0
Chloride (mmol/L)	98.0	102.0–109.0
Lactate (mmol/L)	1.7	0.5–2.2
Amylase (ukat/L)	7.1	0.3–1.6
WBC count (/μl)	39,390	4,000–10,000
Neutrophils	0.80	0.40–0.70
Eosinophils	0.003	0.00–0.60
Basophils	0.002	0.00–0.02
Lymphocytes	0.25	0.20–0.50
Monocytes	0.05	0.04–0.08
Hematocrit	0.44	0.35–0.44
Urinalysis		
Glucose	3+	
Ketones	4+	

WBC = white blood cell.

Table 3. Laboratory data after new diagnosis of diabetes mellitus

	Value	Normal range
HbA1c (Hb fraction)	0.07	0.04–0.06
Anti-GADAb	Neg	
ANA	Neg	
TGB and microsomal Ab	Neg	
IgG (g/L)	8.78	7.00–17.00
IgA (g/L)	1.80	0.70–3.50
IgM (g/L)	1.13	0.50–3.00
C3 (g/L)	1.21	0.83–1.77
C4 (mg/dL)	0.24	0.16–0.47
T3 (nmol/L)	1.68	1.20–2.10
FT4 (pmol/L)	12.70	10.30–21.90
TSH (mIU/L)	2.00	0.34–4.25
TSHRAb	Neg	
C-peptide (nmol/L)	<0.10	0.17–0.66

HbA1c = glycosylated hemoglobin; Anti-GADAb = anti-glutamic acid decarboxylase antibody; ANA = antinuclear antibody; TGB = thyroglobulin; Ig = immunoglobulin; C = complement; T3 = total triiodothyronine; FT4 = free thyroxine; TSH = thyroid stimulating hormone; TSHRAb = thyroid stimulating hormone receptor antibody; Neg = negative.

a case of fulminant type 1 diabetes, as described by Toshiaki Hanafusa in his review on this rare disease, with the key characteristics of near normal glycosylated hemoglobin and very high plasma glucose levels with severe ketoacidosis [5]. The plasma C-peptide level is also markedly decreased. It is probable that a rapid depletion in insulin, coupled with the stress of labor, precipitated diabetic ketoacidosis in this patient with disastrous consequences for the fetus.

The symptoms and signs of fulminant type 1 diabetes with ketoacidosis in pregnancy are similar to those in non-diabetics; however, it has been demonstrated that, during pregnancy, diabetic ketoacidosis can occur at glucose levels as low as 200 mg/dL (normal > 250 mg/dL) [6]. Remarkable symptoms, such as common cold like symptoms and abdominal symptoms, particularly nausea and vomiting with abdominal pain, were pertinent in this case.

The patient did not have a clear history of antecedent viral infection or toxin exposure prior to this event, but a sub-clinical or minimally symptomatic infection could have been present. However, an association between acute islet cell failure and recent viral infection in humans remains purely theoretical. Nevertheless, the onset of fulminant type 1 diabetes is often associated with herpes viruses, enteroviruses such as coxsackie viruses, and echoviruses [7–11].

Although viruses may be the pathogenic agents, a few studies have strongly suggested that certain class II HLA DR4-DQ4 genotypes encoded by DRB1 0405-DQB1 0401 can increase the susceptibility to this disease [12–15].

Immune reactions might also play a role [12–15]. T lymphocytes might respond to glutamic acid decarboxylase, although this does not mean that autoimmunity plays the primary role [16,17]. In the present case, titers for islet cell antibodies were obtained at the time of presentation and were negative. Although this information is not critical to the management of a patient, such tests can enhance our understanding of such cases.

In summary, fulminant type 1 diabetes is a newly discovered subtype of type 1 diabetes that needs special attention because of its rapid rate of onset in apparently healthy subjects, particularly during pregnancy. Diabetic ketoacidosis can be successfully managed during pregnancy if basic principles are followed. The precipitating factors such as accelerated starvation, pregnancy-associated nausea and vomiting, infection, non compliance insulin pump failure, tocolytic agents like beta sympathomimetic drugs and corticosteroids should be identified and corrected, as appropriate.

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中國籍懷孕婦女併發猛爆性第 1 型糖尿病導致流產之病例

李美月[1] 林昆德[1,2] 張毓泓[1,2] 謝明家[1,2,3] 蕭璧容[1,2] 辛錫璋[1,2,3]

[1]高雄醫學大學附設醫院 內科部 內分泌新陳代謝內科

高雄醫學大學 [2]臨床醫學研究所 [3]醫學遺傳研究所

本病例報告一位懷孕 33 週婦女，接受口服葡萄糖耐受測試，結果為正常，卻在短短 11 天後引起糖尿病酮酸血症，導致子宮內胎兒死亡。此可為一件猛爆性第 1 型糖尿病的病例。

關鍵詞：糖尿病酮酸血症，猛爆性第 1 型糖尿病，子宮內胎兒死亡

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高雄醫學大學附設醫院內科部內分泌新陳代謝內科

高雄市三民區自由一路 100 號