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Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 88226

Manuscript Type: CASE REPORT

Case report: Gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus, four cases of double diabetes?

GDM combined with FT1DM.

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Abstract

BACKGROUND

Fulminant type 1 diabetes mellitus (FT1DM) that occurs during pregnancy or the perinatal period is known as pregnancy-related FT1DM (PF), always without history of abnormal glucose metabolism. Here, we present four patients who developed FT1DM during treatment but were first diagnosed with gestational diabetes mellitus (GDM).

CASE SUMMARY

The clinical data of four patients with GDM combined with FT1DM admitted to our hospital between July 2018 and April 2021 were collected, and the patients and their infants were followed up. All patients were diagnosed with GDM during the second trimester and were treated. The blood glucose level elevated suddenly during the third trimester and then were diagnosed with FT1DM. Two patients had an insulin allergy, and two had symptoms of upper respiratory tract infection before onset. One patient developed ketoacidosis, and three developed ketosis. Two patients had cesarean section deliveries, and two had vaginal deliveries. The growth and development of the infants were normal. C-peptide levels were lower than those at onset, suggesting progressive

impairment of islet function. The frequencies of the DRB1*09:01, DQB1*03: 03, DQA1*03:02, DPA1*01:03, DPA1*02:02, DPB1*05:01, DRB4*01:03, G*01:01, and G*01:04 human leukocyte antigen (HLA)-G alleles were high in the present study.

CONCLUSION

In comparison with pregnancy-associated FT1DM (PF), patients with GDM combined with FT1DM had an older age of onset, higher body mass index (BMI), slower onset, fewer prodromal symptoms, and less acidosis. The pathogenesis may be due to various factors affecting the already fragile β -cells of GDM patients with genetically susceptible class II HLA genotypes. We speculate that GDM combined with FT1DM during pregnancy, referred to as “double diabetes,” is a subtype of PF with its own unique characteristics that should be investigated further.

Key Words: fulminant type 1 diabetes mellitus; gestational diabetes mellitus; pregnancy-related fulminant type 1 diabetes mellitus; double diabetes; case report

Li H, Chai Y, Guo WH, Huang Y, Zhang X, Feng W, He Q, Cui J, Liu M. Case report: Gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus, four cases of double diabetes? *World J Clin Cases* 2023; In press

Core Tip: We believe that 4 aspects of this manuscript will make it interesting. First, we reported 4 similar cases first diagnosed with gestational diabetes mellitus (GDM) but then developed Fulminant type 1 diabetes mellitus (FT1DM) during treatment. Second, we summarized the clinical manifestations of the patients with related literature, in comparison with classical pregnancy-related FT1DM(PF). Third, we tested the class II HLA genotype in patients of GDM combined with FT1DM, and discovered the higher frequencies of haplotypes. Finally, we propose that GDM combined with FT1DM as a subtype of PF should be classified as double diabetes occurring during pregnancy.

INTRODUCTION

⁸ Fulminant type1 diabetes mellitus (FT1DM) is a new subtype of type 1 diabetes first proposed by Imagawa in 2000. Its major clinical characteristics include abrupt onset of hyperglycemia within 1 wk, complete β -cell destruction, ketosis or ketoacidosis at onset, and islet-related autoantibody negativity. Pregnant women are at high risk of FT1DM, and FT1DM that occurs during pregnancy or within 2 wk after delivery is considered pregnancy associated FT1DM (PF). Patients with PF often do not have a family history and no previous history of impaired glucose tolerance. Patients demonstrated more severe metabolic disorder and β -cell destruction than diabetes mellitus ketoacidosis (DKA) patients. The sudden onset of insulin deficiency and DKA without warning can be catastrophic for both the mother and fetus and is associated with a very high risk of fetal death.

We identified several patients with both gestational diabetes mellitus (GDM) and FT1DM. These two types of diabetes occurring in the same patient have features that are different from those of classic PF. Herein, we report four patients who were initially diagnosed with GDM who then developed FT1DM during treatment.

CASE PRESENTATION

Chief complaints

Four similar cases have been reported previously. ¹ The first patient was a 29-year-old-woman who was transferred to our hospital in July 2018 at gestational week (GW) 39 with a random blood glucose (BG) level of 20.28 mmol/L and a urinary ketone body level of 3+ (hemoglobin A1C (HbA1c), 6.1%; arterial pH, 7.36). ¹ The second patient was a 27-year-old-woman who was admitted to our hospital in November 2018 with poor BG control three days post-delivery. The third patient was a 28-year-old-woman who was admitted in March 2019 with a sudden increase in her BG level at GW 33+4. ¹ The last patient was a 38-year-old-woman who was admitted to our hospital in January 2021 with an increased BG at GW 37+5.

History of present illness

The first patient was diagnosed with GDM at GW 25, had a fasting blood glucose (FBG) level of 5.65 mmol/L, and began medical nutrition therapy. She started receiving insulin analogs at GW 35, with an FBG of 6.21 mmol/L. Her BG level was much higher than before and required much more insulin at GW 39. She delivered a healthy boy (weight, 3760 g; body length, 52 cm; Apgar score, 10) at GW 39+6 *via* cesarean section. The second patient was diagnosed with GDM at GW 24 and received nutritional therapy. She began treatment with insulin analogs at GW 31, when her FBG was 5.6–6.7 mmol/L. However, she presented with redness and swelling at the injection site two weeks later. The insulin was replaced with human insulin and the allergy symptoms disappeared. She developed fever (38.6°C) at GW 35+3. The FBG increased suddenly to 7.9–10.9 mmol/L at GW 36. She delivered a healthy boy (weight 3390 g; body length, 51 cm; Apgar score, 0) prematurely at GW 36+2. The third patient was diagnosed with GDM at GW 25 and received an insulin analog at GW 29. One week later, she developed redness and swelling at the injection site, and the insulin was replaced with human insulin. A sudden increase in blood glucose was observed, with an FBG of 7.9–10.9 mmol/L. At GW 32, the patient presented with sore throat, rhinorrhea, dizziness, fatigue, nausea, and vomiting; her random BG level was 28 mmol/L, urinary ketone body level was 4+, and arterial pH was 7.29. Consequently, a diagnosis of DKA was made. Laboratory tests indicated a very low C-peptide level, negative GAD and ICA results, and an IAA level of 3.82 U/mL. The patient was treated with an insulin pump; a satisfactory BG level was achieved. She delivered a healthy girl (weight, 3550 g; body length, 50 cm; Apgar score, 10) at GW 38. The insulin pump was continued postpartum; however, the BG levels demonstrated a large degree of fluctuation. The fourth patient was diagnosed with GDM at GW 25, at which time her FBG was 5.9 mmol/L; medical nutrition therapy was initiated. Treatment with insulin analogs was initiated at GW 29 when her FBG was 7.4 mmol/L and HbA1c level was 5.7%. Her BG level was initially well controlled but began to fluctuate significantly, with an FBG level of 8.2–12.2 mmol/L and 2hPG of 7.5–17 mmol/L at GW 37+5. She delivered a healthy boy (weight,

3945 g; body length, 50 cm; Apgar score, 10) at GW 38+5 *via* cesarean section. The random BG level was 21.4 mmol/L, and the urinary ketone body level was 1+ 3 days post-delivery.

History of past illness

All four patients were healthy, with no history of past illness.

Personal and family history

No history of adverse pregnancies was observed for the first patient. For the second patient, an artificial abortion was performed three years ago, and the third patient had a history of artificial abortion eight years ago. The fourth patient underwent artificial abortions in 2015 and 2016. The first and third patients had a family history of type 2 diabetes mellitus (T2DM), while the second and fourth patients had no family history of T2DM.

Physical examination

All four patients had normal blood pressure and BMI levels of 23.24, 30.47, 22.26, and 25.65 kg/m² separately.

Laboratory examinations

In the first patient, 8 wk post labor, the 75-g oral glucose tolerance test (OGTT) demonstrated an extremely low C-peptide level. Tests for antibodies against glutamic acid decarboxylase (GAD) and islet cell antibodies (ICA) were negative. The insulin autoantibody (IAA) titer was 36.93 U/mL (reference range: 0–0.4). At 2.5 years post-delivery, she was pregnant again with negativity for amylase, lipase, ICA, and GAD, and an IAA titer of 5.15 U/mL and her fasting C-peptide level was < 0.01 ng/mL at GW 6 (Table 1). The second patient presented postpartum with fluctuating FBG (9–14 mmol/L), urinary ketone body positivity (3+), and CO₂ combining power of 21 mmol/L (reference range: 21–31 mmol/L). One week post-delivery, the OGTT

demonstrated an extremely low C-peptide level; negativity for GAD, ICA, amylase, and lipase; an IAA titer of > 50 U/mL; and a positive anti-Epstein-Barr virus (EBV) IgG antibody titer. Examination at the 2-year follow-up revealed ICA and GAD negativity and an IAA titer of >50 U/mL. She became pregnant again but underwent elective termination at GW 10. Her fasting C-peptide level was < 0.01 ng/mL 2.5 years later (Table 1). The third patient suffered of same poor islet function, one year later, she was pregnant again and delivered a healthy baby boy (weight, 3340 g; body length, 50 cm; Apgar score, 10) at GW 39. Five months later, she had an IAA titer of 18.59 U/mL, negativity for ICA, GAD, Zinc transporter 8 (ZnT8), and Protein tyrosine phosphatase antibodies (IA-2A), and a fasting C-peptide level < 0.01 ng/mL (Table 1). The fourth patient also underwent an OGTT and demonstrated a low C-peptide level, negativity for GAD, ICA, ZnT8, IA-2A, amylase, or lipase, and an IAA level of 23.2 U/mL soon after delivery (Table 1).

Imaging examinations

Four patients did not conduct any imaging examinations due to pregnancy.

FINAL DIAGNOSIS

All four patients were diagnosed with Gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus.

TREATMENT

Post-delivery, all the four patients received treatment with insulin pumps.

OUTCOME AND FOLLOW-UP

DIAGNOSTIC CRITERIA

The criteria used to diagnose GDM were based on the 2017 China Type 2 Diabetes Prevention Guidelines. GDM was diagnosed when one of the following three findings

was present at any time during pregnancy: 5.1 mmol/L \leq 75-g OGTT FBG level < 7.0 mmol/L; 75-g OGTT 1-h BG level \geq 10.0 mmol/L; 8.5 mmol/L \leq 75-g OGTT 2-h BG level < 11.1 mmol/L. ² The diagnostic criteria for FT1DM were revised by the Committee of the Japan Diabetes Society for the Research of FT1DM in 2012^[4]. According to these criteria, ¹⁰ FT1DM is verified when all of the following are present: the occurrence of diabetic ketosis or DKA within 1 wk post hyperglycemia onset; PG ³ level \geq 16.0 mmol/L and HbA1c level < 8.7% at first diagnostic visit; urinary C-peptide excretion < 10 μ g/d or fasting serum C-peptide level < 0.3 ng/mL (100 pmol/L) and postprandial serum C-peptide level < 0.5 ng/mL (170 pmol/L) at onset.

HLA typing

⁶ Total DNA was extracted from the peripheral blood samples. Allelic groups of the HLA-A*, HLA-B*, HLA-C*, HLA-DQA1*, HLA-DQB1*, HLA-DPA1*, HLA-DPB1*, HLA-DRB1*, HLA-DRB3*, HLA-DRB4*, HLA-DRB5*, and HLA-G* loci were typed using Sanger sequencing (Beijing Genomics Institute, Tianjin, China).

All patients had an onset age of 27–38 years, mean age of 30.5 ± 5.0 years, and mean BMI of 24.73 ± 4.36 kg/m². They were diagnosed with GDM during the second trimester (GW 24–25), and exogenous insulin was initiated for those with unsatisfactory glucose levels. Two patients demonstrated an insulin allergy that manifested as red and itchy skin post insulin injection. The time from allergy to the onset of typical FT1DM symptoms ranges from 20 days to 1 month. FT1DM occurs during the third trimester of pregnancy (GW 32–39) with low C-peptide levels. ¹¹ Flu-like symptoms, including fever, headache, sore throat, cough, and rhinorrhea, were observed in two cases. Urinary ketone body levels ranged from 1+ to 4+. One patient had diabetic ketoacidosis at onset, with an arterial pH of 7.29, whereas the other patients had diabetic ketosis only. Cesarean section was conducted in two patients, while the other two had natural births. Three patients delivered at term, and the fourth delivered preterm. All the fetuses were healthy. Post-delivery, all four patients received treatment with an insulin pump. At the time of onset, all four patients were positive for IAA, but negative for GAD antibody and ICA. Three patients remained positive for IAA 2.5 years post-delivery. C-peptide

levels were even lower than those at the onset, suggesting progressive impairment of islet function (Table 1). HLA genotyping demonstrated high frequencies of DRB1*09:01, DQB1*03:03, DQA1*03:02, DPA1*01:03, DPA1*02:02, DPB1*05:01, DRB4*01:03, G*01:01, and G*01:04 in the present study.

DISCUSSION

Reports of patients with FT1DM have become increasingly common in East Asia. Pregnancy is a risk factor for FT1DM; a nationwide survey in Japan reported that patients with PF accounted for 21% of female FT1DM patients aged 13–49 years. All four patients in this study were diagnosed with GDM during the second trimester, followed by lifestyle intervention and insulin treatment, and the initial BG was well controlled. The patient showed good compliance, and regular self-BG monitoring was conducted, which enabled the timely identification of sudden increases in BG levels. The random plasma glucose level was ≥ 16 mmol/L, while the HbA1c level $< 8.7\%$ with ketosis or ketoacidosis, and the fasting serum C-peptide level < 100 pmol/L (0.3 ng/mL), peak postprandial serum C-peptide level < 170 pmol/L (0.5 ng/mL), and both ICA and GAD negative, indicating a diagnosis of FT1DM. FT1DM that occurs between the start of pregnancy and within 2 wk of delivery is considered PF. Previously reported PF patients had more severe clinical symptoms and metabolic disorders compared with non-pregnant FT1DM patients, including lower arterial pH, lower HbA1c level, and higher blood amylase level, suggesting faster progression and poorer β -cell function in PF patients. The four patients with GDM and FT1DM were different from those with classical PF. The clinical characteristics and laboratory data of three similar cases reported previously and the four patients presented here are summarized and compared with those of patients with classical PF in Table 2.

The patients with GDM combined with FT1DM were older to, and had a higher BMI than, the PF patients. Initially, the BG levels demonstrated satisfactory control; however, they increased with the continuous use of insulin. The difference between these patients and those with classical PF is the vague onset time, which is relatively

mild and slow. At onset, the precursor symptoms were less severe, and the arterial pH was higher than in those with classical PF, indicating mild acidosis. This was likely due to the administration of insulin therapy to GDM patients to avoid serious abnormalities in glucose metabolism. Additionally, these patients had lower fasting C-peptide levels, suggesting poorer β -cell function. All the patients tested positive for IAA. Onset occurred later than GW 32, leading to premature birth or cesarean section. Although four of these seven patients had a premature birth, the infants were generally in good condition with a good prognosis, and all survived. Additionally, postpartum BG level fluctuated markedly, and the patients are prone to hypoglycemia. Choy *et al.* reported a case of FT1DM presenting with rapidly deteriorating glycemic control in the third trimester with insulin-requiring GDM, which was found to be the first report of its kind in the English literature. The symptoms of this patient were similar to those of our study, and she remained on basal-bolus insulin due to persistent β -cell dysfunction. Fortunately, the diagnosis of GDM led to the early recognition of FT1DM and prompt timely treatment, which prevented the development of acidosis and led to positive maternal and neonatal outcomes. Ikeoka *et al.* reported a 27-year-old woman with a history of GDM who developed type 1 diabetes mellitus in the early postpartum period. However, she had GAD-positive type 1 diabetes mellitus and slowly progressive insulin-dependent diabetes mellitus.

Several studies have reported an association between the class II HLA genotype and FT1DM. A study in Japan demonstrated that the frequencies of the DRB1*04:05-DQB1*04:01 and DRB1*09:01-DQB1*03:03 haplotypes were significantly higher in FT1DM patients, whereas the frequency of the DRB1*09:01-DQB1*03:03 haplotype was significantly higher in FT1DM patients with anti-GAD antibodies and in PF patients. The frequencies of DRB1*09:01, DQB1*03:03, DQA1*03:02, DPA1*01:03, DPA1*02:02, DPB1*05:01, DRB4*01:03, G*01:01, and G*01:04 were high in the present study. However, further studies with larger populations are required. We speculated that pregnant women with GDM may already have insulin resistance and β -cell dysfunction due to their genetic background, viral infection, drug hypersensitivity response

syndrome, or other pathogenic factors. Infection or immune reaction may cause the destruction of already fragile β -cells and lead to FT1DM, supporting a “double hit hypothesis.” In GDM, the causal relationship between positive IAA and β -cells destruction is still significantly unknown. Two patients in our study had flu-like symptoms before disease onset, and one was positive for anti-EBV IgG antibodies. Previous studies of PF post viral infections reported that antigen-presenting cells activate T cells *via* Toll-like receptor 3/4, and inflammatory cytokines, including interferon, are delivered to pancreatic β -cells. Regulatory T cells (Tregs) can prevent β -cells destruction by cytotoxic T cells, but the number of Tregs varies during pregnancy, increasing from early pregnancy and decreasing after reaching a peak in the middle of pregnancy. At the end of pregnancy, the number of Tregs is still decreased, which makes the β -cells more susceptible to damage by cytotoxic T cells, and this may be the reason for the increased likelihood of developing FT1DM during pregnancy and immediately post-delivery. Viruses may trigger a transition from helper T-cell 2 to helper T-cell 1 responses, thereby inducing disease. Two of our patients were allergic to insulin, and it has been previously reported that severe drug-induced hypersensitivity syndrome, as a manifestation of drug allergy, can lead to FT1DM and autoimmune thyroid disease, which may be related to decreased Treg numbers and Treg dysfunction. Thus, the etiology of GDM combined with FT1DM is complex and may result from the synergistic effects of multiple factors.

Teupe *et al.* proposed the concept of “double diabetes” in 1991. Pozzilli and Buzzetti described diabetes with both islet autoantibody positivity and characteristics of metabolic syndrome as double diabetes in 2007 and reported cases of double diabetes with FT1DM based on T2DM in Japan in 2013. Patients with double diabetes have clinical features of both T1DM and T2DM^[14]. The combination of GDM with FT1DM, that is, two different types of diabetes, occurs in the same patient during pregnancy and has a lifelong impact. The pathogenesis of GDM is regarded as insulin resistance and β -cell dysfunction, while that of FT1DM includes genetic susceptibility, viral infection, autoimmune component, exogenous insulin antibody syndrome (EIAS), pregnancy, and

drug-induced hypersensitivity syndrome, among others, resulting in β -cell destruction. We propose that GDM combined with FT1DM, as a subtype of PF, has its own characteristics and should be classified as double diabetes occurring during pregnancy. However, ¹² further studies involving a larger number of clinical cases are required to validate these findings.

The present study also found that care is required for the possible development of an insulin allergy during insulin treatment in pregnant women and that patients should be instructed to report any local itching or swelling in a timely manner so that insulin can be replaced or stopped. If the BG level remains significantly elevated post insulin use, especially if it is accompanied by flu-like or gastrointestinal symptoms, routine urine and blood gas analyses should be performed under the supervision of obstetricians and endocrinologists to improve the prognosis of the mother and baby.

CONCLUSION

In summary, GDM combined with FT1DM has features that are different from those of classic PF. It should be classified as double diabetes during pregnancy and recognized by all medical staff, particularly, obstetricians and endocrinologists.

ACKNOWLEDGEMENTS

We thank all the participants who participated in this study and thank the funding from National Natural Science Foundation of China (No. 82270864).

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