ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 February 6; 12(4): 671-871

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 12 Number 4 February 6, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Clinical and Translational Research

Retrospective Study

Observational Study

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 4 February 6, 2024

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 4 February 6, 2024

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 4 February 6, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Che-Chun Su, MD, PhD, Associate Professor, Department of Internal Medicine, Changhua Christian Hospital, Changhua 500, Taiwan. 115025@cch.org.tw

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Si Zhao*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

POLICY OF CO-AUTHORS

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
February 6, 2024

COPYRIGHT
© 2024 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2024 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: office@baishideng.com https://www.wjgnet.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 6; 12(4): 787-794

DOI: 10.12998/wjcc.v12.i4.787

ISSN 2307-8960 (online)

CASE REPORT

Gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus, four cases of double diabetes: A case report

Hui Li, Yun Chai, Wei-Hong Guo, Yu-Meng Huang, Xiao-Na Zhang, Wen-Li Feng, Qing He, Jin Cui, Ming Liu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Imagawa A, Japan; Qureshi W, India

Received: September 16, 2023
Peer-review started: September 16, 2023
First decision: November 30, 2023
Revised: December 13, 2023
Accepted: February 10, 2024
Article in press: January 10, 2024
Published online: February 6, 2024

Hui Li, Yun Chai, Wei-Hong Guo, Yu-Meng Huang, Xiao-Na Zhang, Wen-Li Feng, Qing He, Jin Cui, Ming Liu, Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin 300052, China

Corresponding author: Jin Cui, PhD, Doctor, Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, No. 154 Anshan Road, Heping District, Tianjin 300052, China. cuijin2001@163.com

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, 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

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: We believe that 4 aspects of this manuscript will make it intresting. 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 human leukocyte antigen 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.

Citation: Li H, Chai Y, Guo WH, Huang YM, Zhang XN, Feng WL, He Q, Cui J, Liu M. Gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus, four cases of double diabetes: A case report. *World J Clin Cases* 2024; 12(4): 787-794
URL: https://www.wjgnet.com/2307-8960/full/v12/i4/787.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i4.787

INTRODUCTION

Fulminant type 1 diabetes mellitus (FT1DM) is a new subtype of type 1 diabetes first proposed by Imagawa in 2000[1]. 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-related FT1DM (PF)[2]. 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[3].

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. 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]. 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. 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 BG (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, 10) 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 BG 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 glutamic acid decarboxylase (GAD) and islet cell antibodies (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 2 h postprandial glucose (PG) 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 d 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 body mass index (BMI) levels of 23.24, 30.47, 22.26, and 25.65 kg/m^2 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 GAD and 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 CO_2 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) immunoglobulin G (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 GDM 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 ≤ 75-g OGTT FBG level < 7.0 mmol/L; 75-g OGTT 1-h BG level ≥ 10.0 mmol/L; 8.5 mmol/L ≤ 75-g OGTT 2-h BG level < 11.1 mmol/L. 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, FT1DM is verified when all of the following are present: the occurrence of diabetic ketosis or DKA within 1 wk post hyperglycemia onset; PG level ≥ 16.0 mmol/L and HbA1c level < 8.7% at first diagnostic visit; urinary C-peptide excretion < 10 μg/d or fasting serum C-peptide level < 0.3 ng/mL (100 pmol/L) and

Table 1 Clinical data of 4 cases of gestational diabetes mellitus combined fulminant type 1 diabetes mellitus in our hospital

Case	Time	IAA (0-0.4)	HbA1c	Glucose (mmol/L)			Insulin (mU/L)			C-peptid (ng/mL)		
				0 min	60 min	120 min	0 min	60 min	120 min	0 min	60 min	120 min
1	P 25 wk		5.4	5.65								
	Post 8 wk	36.93	6.7	5.37	17.73	25.89	> 300	> 300	> 300	0.01	< 0.05	0.18
	Post 6 months		6.5	9.56	22.69	30.25	28.3	29.6	28.1	0.07	0.14	0.16
	Post 1 yr	> 50		5.54			43.6			0.02		
	Post 2.5 yr	5.15	6.6									
	Post 2.7 yr		5.8	3.52			8.3			< 0.01		
2	P 24 wk		6.1	5.2	8.54	6.51						
	Post 1 wk	> 50	6.2	7.95	18.02	23.44	44.5	17.3	14.7	0.02	< 0.05	< 0.05
	Post 6 months		7	7.3	12.63	16.46	21.7	22.2	21.9	0.01	0.01	0.01
	Post 1yr	5.5	7.6	10.89	19.04	25.4	21.4	21.1	19.4	< 0.01	< 0.01	< 0.01
	Post 2.5 yr	> 50	6.6	3.92			10.8			< 0.01		
3	P 25 wk			5.4	11.18	10.47	16.8	106.4	175.1			
	P 33 wk	3.82	6.1	5.03	12.1	18.7	18.7	10.4	7.3	0.04	< 0.05	0.14
	Post 5 months	18.59	5.7	7.67			116.3			0.01		
4	P 25 wk			5.9								
	P 29 wk		5.7									
	Post 3 d	23.2	6.1	10.46	22.07	26.82	14.1	10.4	9.9	0.13	0.27	0.51
	Post 3 months			9.1	21	25.8	< 0.2	1.03	3.08	0.06	0.207	0.435

P: Pregnant; Post: Postpartum; IAA: Insulin autoantibody; HbA1c: Hemoglobin A1C.

postprandial serum C-peptide level < 0.5 ng/mL (170 pmol/L) at onset.

HLA typing

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/m^2. 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 d to 1 month. FT1DM occurs during the third trimester of pregnancy (GW 32-39) with low C-peptide levels. 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[5] 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*[6] 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*[7] 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. Ting Tai *et al*[8] reported a case of a GDM mother complicated with FT1DM immediately post-delivery in 2022, which highlighted again that FT1DM not only can occur in pregnancy with normal glucose tolerance but can also complicate mother with GDM.

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[9]. 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

Table 2 Clinical characteristics of pregnancy-related fulminant type 1 diabetes mellitus *vs* gestational diabetes mellitus combined with fulminant type 1 diabetes mellitus

	PF (*n* = 105, pregnant *n* = 80, postpartum *n* = 25)	GDM combined with FT1DM (*n* = 7, pregnancy *n* = 5, postpartum *n* = 2)
Age of onset age, (range value)	27.9 (21-38)	31.6 (27-40)
BMI [kg/m^2, (range value)]	22.1 (16.9-29.5)	23.4 (16.85-30.47)
Number of weeks of pregnancy		
Pregnancy [week, (range value)]	26.2 (6-38)	36.3 (33-40)
Postpartum days [days, (range value)]	6.4 (1-15)	7.3 (3-13)
Start time [day, (range value)]	3.2 (1-9)	----
Family history (-/+)	55/9	3/4
Fetal survival (survival/ total)	13/58	7/7
Clinical manifestations		
Influenza-like symptoms (%)	50 (47/94)	42.8 (3/7)
Gastrointestinal symptoms (%)	59.5 (56/94)	42.8 (3/7)
Fever: (%)	26.7 (8/30)	0/7
Consciousness disorders (%)	43.3 (13/30)	0/7
Laboratory examination		
PH (range)	7.07 (6.91-7.4)	7.20 (7.08-7.36)
HbA1c [% (range value)]	6.26 (4.8-8.7)	5.92 (5.4-6.2)
Blood sugar [mmol/L, (range value)]	37.13 (16.6-78.5)	22.05 (16.0-44.9)
PG/HbA1c ratio	5.29	3.76
Fasting C Peptide (ng/mL)	0.07	< 0.04
Afteral C Peptide (ng/mL)	0.11	< 0.13
GAD (-/+)	87/7	7/0
IAA (-/+)	---	0/7 (positive at 4 cases and 3 cases positive after treatment)
Transsusceptible genotypes	HLADRB1 09:01-DQB1 03:03 (DR9)	HLADRB1 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

PF: Pregnancy-related fulminant type 1 diabetes mellitus; GDM: Gestational diabetes mellitus; FT1DM: Fulminant type 1 diabetes mellitus; BMI: Body mass index; HbA1c: Hemoglobin A1C; PG: Postprandial glucose.

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[10]. 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[11].

Teupe *et al*[12] proposed the concept of "double diabetes" in 1991. Pozzilli and Buzzetti[13] 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[14]. Patients with double diabetes have clinical features of both T1DM and T2DM[15]. 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, 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, 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.

FOOTNOTES

Co-corresponding authors: Jin Cui and Ming Liu.

Author contributions: Li H analyzed data and wrote the paper; Chai Y collected data and performed research; Guo WH collected data; Huang YM collected data and revised the manuscript; Zhang XN collected data; Feng WL analyzed data and revised the manuscript; He Q performed research and supervision; Cui J designed the study and revised the paper; Liu M designed the study and analyzed data. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Cui J and Liu M contributed equally to this work as co-corresponding authors. The reasons for designating Cui J and Liu M as co-corresponding authors are twofold. First, all the work was done under the instructions of Cui J and Liu M. The designation of co-corresponding authors accurately reflects the equal contribution to this work, this collaboration helps share knowledge and resources, improve the quality and efficiency of our research. Second, the corresponding authors bear ultimate responsibility for the accuracy and integrity of the paper, co-corresponding authors can clarify everyone's contributions and responsibilities, avoid potential disputes or misunderstandings. In summary, we believe that designating Cui J and Liu M as co-corresponding authors is fitting for our manuscript, which can promote academic collaboration, clarify responsibilities and contributions, thereby improving research quality and academic influence.

Supported by National Natural Science Foundation of China, No. 82270864.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Hui Li 0000-0003-1952-9994; Wei-Hong Guo 0000-0002-7781-2432; Jin Cui 0000-0003-1546-1830; Ming Liu 0000-0003-2665-4072.

S-Editor: Qu XL
L-Editor: A
P-Editor: Qu XL

REFERENCES

1 **Imagawa A**, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. *N Engl J Med* 2000; **342**: 301-307 [PMID: 10655528 DOI: 10.1056/NEJM200002033420501]

2 **Imagawa A**, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Toyoda T, Maruyama T, Makino H. Fulminant type 1 diabetes: a nationwide survey in Japan. *Diabetes Care* 2003; **26**: 2345-2352 [PMID: 12882860 DOI: 10.2337/diacare.26.8.2345]

3 **Liu L**, Jia W, Liu R, Shen J. Clinical study of pregnancy-associated fulminant type 1 diabetes. *Endocrine* 2018; **60**: 301-307 [PMID: 29500601 DOI: 10.1007/s12020-018-1556-x]

4 **Imagawa A**, Hanafusa T, Awata T, Ikegami H, Uchigata Y, Osawa H, Kawasaki E, Kawabata Y, Kobayashi T, Shimada A, Shimizu I, Takahashi K, Nagata M, Makino H, Maruyama T. Report of the Committee of the Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus: New diagnostic criteria of fulminant type 1 diabetes mellitus (2012). *J Diabetes Investig* 2012; **3**: 536-

539 [PMID: 24843620 DOI: 10.1111/jdi.12024]

5 **Wu H**, Yu M, Xiao C, Li NS, Fu Y, Mao JF, Ping F, Li W, Liu W, Li YX, Xiao XH. Clinical characteristics of pregnancy-associated fulminant type 1 diabetes--a single center experience. *Zhonghua Tangniaobing Zazhi* **11**: 720-724 [DOI: 10.3760/cma.j.issn.1674-5809.2019.11.005]

6 **Choy KHA**, Wong T, Cao RHM, Flack JR. Fulminant type 1 diabetes mellitus in a GDM pregnancy: early recognition is vital for maternal and fetal outcomes. *Endocrinol Diabetes Metab Case Rep* 2022; **2022** [PMID: 35899692 DOI: 10.1530/EDM-22-0262]

7 **Ikeoka T**, Sako A, Kuriya G, Yamashita H, Yasuhi I, Horie I, Ando T, Abiru N, Kawakami A. Type 1 Diabetes Mellitus Diagnosed during Follow-up of Gestational Diabetes Mellitus in the Early Postpartum Period. *Intern Med* 2018; **57**: 3413-3418 [PMID: 30101928 DOI: 10.2169/internalmedicine.1188-18]

8 **Ting Tai Y**, Mohd Noor N. A rare case of a mother with gestational diabetes complicated with fulminant type 1 diabetes mellitus post-delivery. *J R Coll Physicians Edinb* 2022; **52**: 120-123 [PMID: 36147001 DOI: 10.1177/14782715221103668]

9 **Zheng C**, Zhou Z, Yang L, Lin J, Huang G, Li X, Zhou W, Wang X, Liu Z. Fulminant type 1 diabetes mellitus exhibits distinct clinical and autoimmunity features from classical type 1 diabetes mellitus in Chinese. *Diabetes Metab Res Rev* 2011; **27**: 70-78 [PMID: 21218510 DOI: 10.1002/dmrr.1148]

10 **Shimizu I**, Makino H, Imagawa A, Iwahashi H, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Maruyama T, Hanafusa T. Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy. *J Clin Endocrinol Metab* 2006; **91**: 471-476 [PMID: 16278271 DOI: 10.1210/jc.2005-1943]

11 **Marchese M**, Leinung M, Shawa H. Drug-induced hypersensitivity reaction: A case of simultaneous thyroiditis and fulminant type 1 diabetes. *Avicenna J Med* 2017; **7**: 67-70 [PMID: 28469989 DOI: 10.4103/ajm.AJM_124_16]

12 **Teupe B**, Bergis K. Epidemiological evidence for "double diabetes". *Lancet* 1991; **337**: 361-362 [PMID: 1671252 DOI: 10.1016/0140-6736(91)90988-2]

13 **Pozzilli P**, Buzzetti R. A new expression of diabetes: double diabetes. *Trends Endocrinol Metab* 2007; **18**: 52-57 [PMID: 17208448 DOI: 10.1016/j.tem.2006.12.003]

14 **Ogawa A**, Niiya T, Manabe K, Kawamoto E. [Fulminant type 1 diabetes in an elderly patient treated after receiving a diagnosis of type 2 diabetes]. *Nihon Ronen Igakkai Zasshi* 2013; **50**: 818-823 [PMID: 24622231 DOI: 10.3143/geriatrics.50.818]

15 **Kietsiriroje N**, Pearson S, Campbell M, Ariëns RAS, Ajjan RA. Double diabetes: A distinct high-risk group? *Diabetes Obes Metab* 2019; **21**: 2609-2618 [PMID: 31373146 DOI: 10.1111/dom.13848]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2024 Baishideng Publishing Group Inc. All rights reserved.