

Fulminant type 1 diabetes mellitus in a GDM pregnancy: early recognition is vital for maternal and fetal outcomes

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Summary

Fulminant type 1 diabetes mellitus (FT1DM) is characterised by extremely rapid destruction of pancreatic beta cells. An association between FT1DM and pregnancy has been reported and can lead to unfavourable pregnancy outcomes without timely treatment. We report a case of FT1DM in a pregnancy with gestational diabetes mellitus (GDM), the first of its kind in the English literature to date. A 27-year-old woman with insulin-requiring GDM presented with rapidly deteriorating glycaemic control in her third trimester of pregnancy despite good concordance to treatment. The investigation identified the hallmarks of FT1DM: hyperglycaemia with acute metabolic decompensation and non-immune-mediated beta-cell failure. She received prompt treatment with intravenous insulin therapy and was transitioned to subcutaneous insulin once biochemical improvement had been achieved, albeit with higher insulin requirements than before. She had a good pregnancy outcome and delivered a healthy male infant 5 weeks later through induction of labour. Due to persistent beta-cell dysfunction, she remained on basal-bolus insulin postpartum. This case highlights the importance of early recognition and treatment of FT1DM in pregnancy to prevent adverse maternal and fetal prognoses.

Learning points

- Fulminant type 1 diabetes mellitus (FT1DM) is a subtype of type 1 diabetes characterised by extremely rapid beta-cell destruction, leading to abrupt-onset hyperglycaemia with ketosis or ketoacidosis.
- The pathognomonic characteristics of FT1DM include the development of diabetic ketosis or ketoacidosis typically within 7 days after the onset of symptoms of hyperglycaemia, a near-normal level of glycated haemoglobin despite elevated plasma glucose levels and the absence of islet cell autoantibodies.
- The pathophysiology of FT1DM is unclear but the association with genetic predisposition, viral infection and pregnancy has been reported.
- Due to its predilection for pregnancy, clinicians should have a high index of suspicion for FT1DM in pregnant women with rapidly progressing hyperglycaemic ketoacidosis.
- As diabetic ketoacidosis in pregnancy is associated with adverse maternal and fetal outcomes, immediate initiation of treatment in pregnant women with suspected FT1DM is extremely vital to prevent morbidity and mortality, even if investigations are still underway.
- Patients with FT1DM require lifelong insulin therapy due to the complete loss of beta-cell function.



Background

Fulminant type 1 diabetes mellitus (FT1DM) is a distinct subtype of type 1 diabetes mellitus in which the process of beta-cell destruction is extremely rapid, predisposing to abrupt onset of hyperglycaemia and ketosis or ketoacidosis. The clinical characteristics of FT1DM differ from those of autoimmune type 1 diabetes mellitus. Without prompt treatment, FT1DM with metabolic decompensation can lead to a fatal outcome. FT1DM is rare outside of East and South East Asia. An association between FT1DM and pregnancy is well documented in the literature. We present a case of FT1DM in a woman with gestational diabetes mellitus (GDM), highlighting its clinical manifestations and pathophysiology, as well as the implications of delayed treatment in pregnancy.

Case presentation

A 27-year-old gravida 2, para 1 woman of Southeast Asian ethnicity, was diagnosed with recurrent GDM on early 75-g glucose tolerance testing at 16 weeks gestation. Glycated haemoglobin (HbA1c) was 5.1%. Pre-pregnancy BMI was 32.8 kg/m². She had no personal or family history of an autoimmune disorder. Insulin was commenced at 22 weeks gestation, with fortnightly dose adjustment to achieve glycaemic targets. At 33 weeks gestation, at which time she was on insulin isophane (Protaphane®) 28 units once every night and insulin aspart (NovoRapid®) 4 units thrice daily, her glycaemic management rapidly deteriorated despite excellent concordance to insulin and lifestyle management. Blood glucose levels (BGLs) worsened from an initial range from 5–8 mmol/L to 10–20 mmol/L in less than a week. She had also experienced new-onset polydipsia but reported no fevers or symptoms suggestive of an infection. There was no nausea, vomiting or abdominal pain. She had appropriate weight gain throughout her pregnancy. Maternal haemodynamics, fetal movements and cardiotocography were normal.

Investigation

Bedside capillary BGL was 15 mmol/L, associated with a raised ketone level of 0.8 mmol/L (range: <0.6 mmol/L). Biochemistry and venous blood gas demonstrated no evidence of acidosis. C-peptide level in the context of hyperglycaemia was inappropriately low (98 pmol/L, range: 260–1400 pmol/L), suggesting beta-cell failure. Repeat HbA1c was 6.3%. White cell count, C-reactive protein, renal function, electrolytes and thyroid function

test were normal. Serum lipase level was mildly elevated at 88 U/L (range: 13–60 U/L) and serum amylase level was normal. Antibodies to glutamic acid decarboxylase and islet antigen-2 were not detected. Fetal growth scan revealed normal growth parameters and amniotic fluid index.

Treatment

Intravenous insulin infusion and intravenous fluid therapy were promptly initiated, leading to a gradual improvement in BGLs and ketosis. She was transitioned to subcutaneous insulin following resolution of hyperglycaemia and ketosis 48 h later, albeit with significantly higher insulin requirements than before: insulin detemir (Levemir®) 30 units in the morning, 30 units at midday and 50 units at night, in addition to insulin aspart (NovoRapid®) 26 units three times a day.

Outcome and follow-up

She was discharged home once her BGLs were stable and attended weekly outpatient appointments for insulin dose adjustment. Her glycaemic control remained within target over the subsequent weeks. She underwent a successful induction of labour at 38 weeks gestation, delivering a male infant with a birth weight of 3636 g and Apgar scores of 2 (1 minute), 5 (5 min) and 8 (10 min). Beta-cell dysfunction persisted postpartum as evidenced by subnormal C-peptide levels of 74 pmol/L, range 260–1400 pmol/L) and 22 pmol/L (with a paired serum glucose of 11.3 mmol/L) at 2 and 20 weeks postpartum, respectively, necessitating ongoing treatment with basal-bolus insulin. The association between class II HLA genes and FT1DM prompted a subsequent assessment with HLA typing which revealed class II DRB1*07:01-DQB1*02:02 haplotypes.

Discussion

FT1DM was first described in Japan in 1987 and has since been reported in other parts of the world, predominantly in East Asia and Southeast Asia (1, 2, 3, 4, 5). The incidence of fulminant type 1 diabetes in Caucasians is relatively low (2). To the best of our knowledge, the occurrence of FT1DM in pregnancy has only been reported in patients of East Asian or Southeast Asian ethnicity (1, 2, 3, 4, 5), and our case represents the only case of FT1DM occurring in a pregnancy with GDM reported in the English literature thus far. The extremely rapid beta-cell destruction and abrupt development of hyperglycaemia associated with

FT1DM are in stark contrast to autoimmune type 1 diabetes, which progresses slowly and takes at least several years from the initial appearance of autoantibodies in the peripheral blood to the clinical onset of disease (Figs 1 and 2). The duration from normal beta-cell function to the almost complete destruction of beta cells in FT1DM ranges from a few days to less than a week (6).

A set of diagnostic criteria for FT1DM was first proposed in 2004 and this was revised by Imagawa *et al.* in 2012. FT1DM is confirmed when these findings are present: the occurrence of diabetic ketosis or ketoacidosis within 7 days after the onset of hyperglycaemic symptoms; elevation of urinary and/ or serum ketone bodies at first visit; plasma glucose level ≥ 16.0 mmol/L and HbA1c level $< 8.7\%$ at first visit; and very low urinary C-peptide excretion or serum C-peptide level. Islet autoantibodies, such as antibodies to glutamic acid decarboxylase and islet antigen-2 are generally not detected (7). Raised serum pancreatic enzyme levels are common findings in these patients, especially in the context of diabetic ketoacidosis, and may be non-specific or reflect pancreatic inflammation (4, 7). Therefore, careful interpretation of serum pancreatic enzyme levels along with focused history and the aid of relevant imaging if indicated are essential to exclude acute pancreatitis, a potential cause of diabetic ketoacidosis or acute deterioration in glycaemic control. Serum lipase or amylase levels in pancreatitis are usually at least three times greater than the upper limit of normal (8). HbA1c level is unreliable in the evaluation of FT1DM as it does not increase during the acute phase (5).

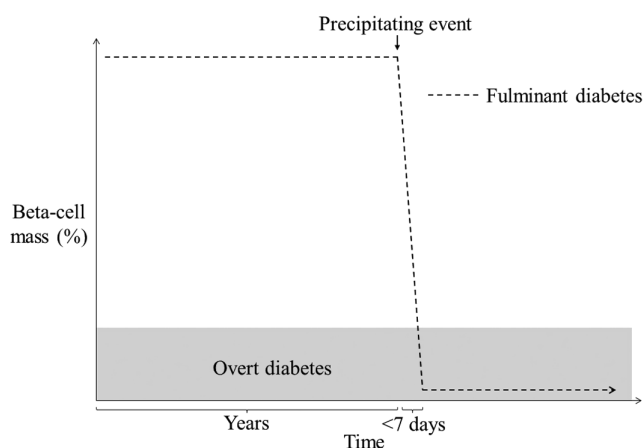


Figure 1 Schematic process comparing the trajectory of beta-cell loss in fulminant type 1 diabetes to autoimmune type 1 diabetes (figure 2). (Adapted from: Hanafusa T, Imagawa A. Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. *Nat Clin Pract Endocrinol Metab.* 2007; 3: 36–45.)

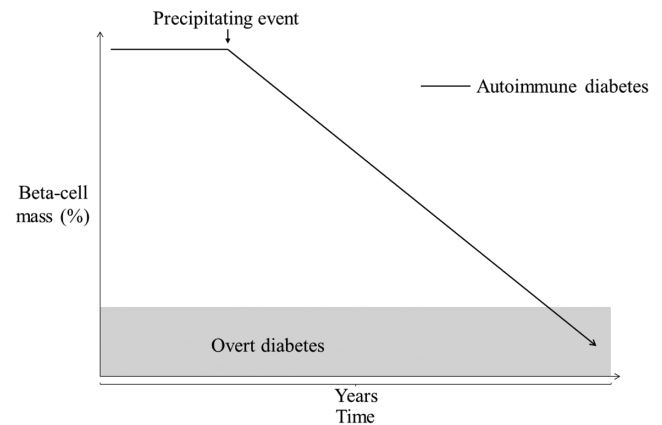


Figure 2 Trajectory of beta-cell loss in autoimmune type 1 diabetes. (Adapted from: Hanafusa T, Imagawa A. Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. *Nat Clin Pract Endocrinol Metab.* 2007; 3: 36–45.)

Our patient exhibited the characteristics of FT1DM: abrupt-onset hyperglycaemia, ketosis, negative islet autoantibodies and a subnormal C-peptide level. She lacked the signs and symptoms of acute pancreatitis and the marginal elevation in her lipase level was not suggestive of pancreatitis. Hyperglycaemia with metabolic decompensation in pregnancy contributes to adverse maternal outcomes (9) and a high rate of fetal demise, with reported perinatal mortality ranging from 9 to 35% even with intensive therapy (3, 4). A myriad of mechanisms by which maternal diabetic ketoacidosis affects the fetus have been suggested, including maternal dehydration causing reduced uteroplacental blood flow and maternal acidosis with resultant fetal acidosis (3). During pregnancy, diabetic ketoacidosis occurs at lower glucose levels and progresses more rapidly than in the non-gravid state (4). Moreover, in a study by Shimizu *et al.* comparing the clinical characteristics of pregnant women with FT1DM with non-pregnant FT1DM women, there was more severe acidosis at the onset of FT1DM in the former group, attributable to accelerated starvation due to hormonal and metabolic changes in pregnancy (3). Fortunately, the diagnosis of GDM in our patient led to early recognition of FT1DM and prompt initiation of intravenous insulin infusion, which prevented the development of acidosis and led to positive maternal and neonatal outcomes.

The pathophysiology of FT1DM is incompletely understood but both environmental and genetic susceptibility have been suggested. The role of autoimmunity remains uncertain (1, 3, 4). A characteristic of FT1DM is its predilection for pregnancy with the onset of diabetes typically in the third trimester, as



seen in our patient, or immediately after delivery. A nationwide study conducted in Japan revealed that approximately one-fifth of cases of FT1DM occurred in pregnant women – equivalent to a rate 14 times greater than that of typical type 1 diabetes (2, 4) – and almost all patients who developed type 1 diabetes during pregnancy appeared to have FT1DM (2). Significant changes in the immunological milieu during pregnancy may be a factor (3, 7).

Viral infection has also been strongly suggested to play a role in the development of FT1DM in both pregnant and non-pregnant patients, as evidenced by flu-like symptoms or gastrointestinal symptoms preceding the disease onset in 70% of patients (3, 4). Those implicated include enteroviruses and herpes virus (1, 4). Viral infections are thought to cause rapid pancreatic beta-cell destruction (1, 3). Epidemiological studies have indicated that enteroviruses have a strong tropism for insulin-producing beta-cells and the destruction of these cells leads to type 1 diabetes mellitus (1).

HLA class II genes, especially the DRB1 and DQB1 haplotypes, have been implicated in FT1DM. HLA class II genotypes DRB1*04:05-DQB1*04:01 confer susceptibility to the development of FT1DM. However, the frequency of DRB1*09:01-DQB1*03:03 is reported to be higher in pregnant women with FT1DM than in non-pregnant patients (3). The higher population frequency of the HLA-DR4-DQ4 haplotype in the East Asian populations may explain the higher incidence of FT1DM in these countries (4). HLA typing in our patient demonstrated class II DRB1*07:01-DQB1*02:02, which, to the best of our knowledge, has not been reported to confer susceptibility to FT1DM in the literature (1, 3, 4, 7).

It is imperative that clinicians especially obstetricians, endocrinologists and general practitioners be aware of FT1DM and have a high index of suspicion for this condition in patients presenting with rapid-onset hyperglycaemia or symptoms of hyperglycaemia during pregnancy or immediately postpartum. Early recognition and treatment of FT1DM is crucial in preventing unfavourable pregnancy outcomes. However, the prediction of the onset of this disease presents a challenge, due to the abrupt onset and lack of familial or personal history of glucose intolerance in this subset of women. Polydipsia, new-onset dyspnoea, marked fatigue, nausea and decreased fetal movements are among the reported manifestations accompanying the onset of FT1DM diabetes in pregnancy (1, 4, 6). Nausea, dyspnoea and fatigue may be mistaken for symptoms related to pregnancy and should not be overlooked (10). In those with GDM, an unexplained acute deterioration in

glycaemic control should prompt an urgent assessment for FT1DM.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

Author contribution statement

Kay Hau Aaron Choy is the primary author involved in literature review and manuscript preparation. Tang Wong is the primary physician responsible for the care of the patient and contributed to revision of the manuscript. Rena Cao was involved in literature review and drafting of the manuscript. Jeff Flack was involved in the care of the patient and contributed to the revision of the manuscript. All authors have read and approved the final version of the manuscript.

References

- 1 Hayakawa T, Nakano Y, Hayakawa K, Yoshimatu H, Hori Y, Yamanishi K, Yamanishi H, Ota T & Fujimoto T. Fulminant type 1 diabetes mellitus associated with coxsackievirus type B1 infection during pregnancy: a case report. *Journal of Medical Case Reports* 2019 **13** 186. (<https://doi.org/10.1186/s13256-019-2130-8>)
- 2 Imagawa A, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Toyoda T, Maruyama T, *et al.* Fulminant type 1 diabetes: a nationwide survey in Japan. *Diabetes Care* 2003 **26** 2345–2352. (<https://doi.org/10.2337/diacare.26.8.2345>)
- 3 Shimizu I, Makino H, Imagawa A, Iwahashi H, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Maruyama T, *et al.* Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 471–476. (<https://doi.org/10.1210/jc.2005-1943>)
- 4 Farrant MT, Rowan JA & Cundy T. Fulminant type 1 diabetes in pregnancy. *Internal Medicine Journal* 2016 **46** 1212–1215. (<https://doi.org/10.1111/imj.13218>)
- 5 Li CY, Li Y, You ZY, Liu YR, Wang YJ, Mu T, Zhao CZ, Yi ZM & Zhang YW. Fulminant type 1 diabetes mellitus in pregnancy. *Brazilian Journal of Medical and Biological Research* 2020 **53** e9633. (<https://doi.org/10.1590/1414-431x20209633>)
- 6 Hanafusa T & Imagawa A. Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. *Nature Clinical Practice: Endocrinology and Metabolism* 2007 **3** 36–45; quiz 2p following 69. (<https://doi.org/10.1038/ncpendmet0351>)
- 7 Imagawa A, Hanafusa T, Awata T, Ikegami H, Uchigata Y, Osawa H, Kawasaki E, Kawabata Y, Kobayashi T, Shimada A, *et al.* 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). *Journal of Diabetes Investigation* 2012 **3** 536–539. (<https://doi.org/10.1111/jdi.12024>).

8 Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS & Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013 **62** 102–111. (<https://doi.org/10.1136/gutjnl-2012-302779>)

9 Kamalakannan D, Baskar V, Barton DM & Abdu TA. Diabetic ketoacidosis in pregnancy. *Postgraduate Medical Journal* 2003 **79** 454–457. (<https://doi.org/10.1136/pmj.79.934.454>)

10 Zib M, Lim L & Walters WA. Symptoms during normal pregnancy: a prospective controlled study. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 1999 **39** 401–410. (<https://doi.org/10.1111/j.1479-828x.1999.tb03122.x>)

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