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SuccessfulSecundigravidainFulminantType1DiabetesMellitus:ACaseReport

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1. Abstract

Purpose: Topresentawomanwithsuccessfulsecundigravida after being diagnosed fulminant type 1 diabetes mellitus.

Method: Adescriptive case report of a single patient.

Results: A healthy baby girl was delivered by Caesarean section. A 33-year-old woman, at 34 weeks and five days of her first pregnancy, was admitted to our hospital with severe nausea, vomiting,diarrheaandstomachache.Shewassubsequentlydiagnosedas FT1DMbasedonsignificantlyhighbloodsugar,normal HbA1c, positive ketones, absolute deficiency in insulin secretion andnodiabeticautoantibodies.Inductionoflabourwasperformed duetostillbirth,bloodglucosewaswellcontrolledwithlong-term insulin therapy and no diabetes-related complications have been identified to date.After five years, the patient recently has a suc- cessful secundigravida by naturally conception and delivery.

Conclusions: Despite FT1DM is a rare disease. Herein, this casewassuccessfulsecondpregnancyanddeliveryfiveyearsafter the diagnosis of FT1DM, with the aim of obtaining widespread attention to FT1DM patients, providing the patients with more consultingontheirpregnancysuggestionwhichmightgetadverse outcomes reduce

2. Introduction

As a result of the vast majority of the destruction of pancreatic beta-cellsshortly,Fulminanttype1diabetesmellitus(FT1DM)is infrequentanddistinguishedthoughtheadvancementofhyperg-

lycemia and diabetic ketoacidosis (DKA) [1]. The mechanism of FT1DMisunknownandmayberelatedtothepregnancy,autoimmunity, hereditary susceptibility, and viral infection. Herein, we reported a case of FT1DM infected by Coxsackievirus type B1 infectionduringthefirstpregnancycausingintrauterinestillbirth, whohadsuccessfulsecundigravidafiveyearslater.Thisisthefirst case report of a woman who had successful secundigravida and delivery after being diagnosed with FT1DM.

3. Case History

A33-year-old female patient, G1P0 (G: gestation, P: parturition) denied a family history of diabetes. No abnormalities were found inhermedicalexaminationduringherpregnancy.Shehadundergone a 75-g oral glucose tolerance test at the 28th week of gestation, which was normal. On Aug 15, 2016, 34 weeks and five daysofgestation, shedevelopednausea,vomiting,stomachache and diarrhea for about half a day, without seeking any medical help. One hour later, the patient's symptoms deteriorated and she suffered from dyspnea. She was taken to a general hospital but withundiagnosed.Thereafter,shewastransferredtotheemergency department of our hospital. On admission, laboratory results showed that fingertip blood glucose was high (≥33.3 mM), urine ketone and glucose both were 4+, blood pH was 7.1. Other statistics were shown in (Table 1). Vital signs: temperature,37.5°C; pulse rate,110 beats per minute; respiratory rate, 28 breaths minute;andbloodpressure,150/90mmHg.Examinationrevealedfetal bradycardia.ThepatientwasdiagnosedwithDKAandintrauterine

stillbirth.And was immediately given effective fluid infusion, intravenousinsulin,anti-infectiontomaintainvitalsigns.Multi-disciplinary treatment (obstetrics, endocrinology and anesthesiology departments) was conducted immediately, and the patient was transferred to the ICU after induction of labour. In the ICU, her blood glucose fluctuated greatly (4.5-27.5 mM), with continuous intravenous insulin infusion.Aweek later, she was transferred to theendocrinologydepartment,herfingertipbloodglucoseranged from5.3to22.6mM,andketonewasnegativewithinsulinpump. Thelaboratoryexaminationresultsarereportedin(Table1).Acute pancreatitis was excluded by abdominal CT scan. From Aug 23, daily multiple injections of insulin aspart (Novonordisk, Denmark) and insulin lantus (Sanofi, France) were administered, instead of insulin pump. After 14 days of treatment, she recovered andwasdischargedfromthehospital.Duringthefiveyears,many C-peptidereleasingtestsconfirmedthatfastingC-peptidewas <0.01ng/mL,andpostprandial2hC-peptidewasalso<0.01ng/mL thefluctuationofglucoserangedfrom4.0to20mM，andnodiabetes-relatedcomplicationsoccurred.Hermenstruationstoppedin May2021,shefoundshewaspregnantandHbA1c6.5%.Doppler ultrasonography suggested visible fetal heartbeat and intrauterine live fetus at the beginning of September (Figure 1A). On Dec 15, four-dimensional color ultrasound indicated that the gestational week of the fetus was 22 weeks, and the gestational week was 22 and5daysaccordingtothelastmenstruation.Thesizeofthefetus by color Doppler ultrasound was consistent with the actual gestationalweek(Figure1B).OnMar25,2022,shegavebirthtoababy girlwithaweightof3200g.Otherparametersareshownin(Table 1). The Apgar score was 10 points in the first minute, 10 pointsin the fifth minute and 10 points in the tenth minute. The blood insulindosageandglucoselevelsbeforeconception,theperiodof conception and after delivery in the second pregnancy are shown in (Figure 2).

Table1: Thelaboratoryexaminationresultsinthefirstandsecondpregnancy

	Aug15,2016(first pregnancy)	**Aug22,2016(first pregnancy)**	**Mar25,2022(second pregnancy)**
RBC (4.3-5.8^12/L)	4.1*10^12/L	5.3*10^12/L	4.1*10^12/L
WBC(3.5-9.5*10^9/L)	13.8*10^9/L	4.8*10^9/L	5.2*10^9/L
HB(130-175G/L)	108	95	108
NEUT	12.0*10^9/L	2.21*10^9/L	2.41*10^9/L
PLT(100-300*10^9/L)	224*10^9/L	98*10^9/L	115*10^9/L
Hcrp(0-10mg/dl)	55	8.5	11
ESR(0~20mm/h)	95	8	9
CoxsackievirusB1	positive	NA	NA
ALT(9-50U/L)	56	51	45
AST(15-40U/L)	85	53	32
TP(65-85g/L)	68.5	55	61.5
K+ (3.5-5.5mmol/L)	5.24	3.8	4.2
Na+ (135-145mmol/L)	140.2	135.3	132.2
Cl- (99-110mmol/L)	100.7	89.4	95.7
Ca2+ (2.10-2.55mmol/L)	2.05	2.17	2.2
Amylase (20-52U/L)	57.6	30.2	12.6
Lipase(5.6-35U/L)	32.3	27.4	24.3
Crea(58-110umol/L)	88	56	56
glucose(3.9-6.1)mmol/L	34.95	6.8	5.7
Blood Ketone	positive	Negative	Negative
Fasting C-peptide (0.78-1.89ng/mL)	<0.01	<0.01	<0.01
2h C -peptide (0.78-1.89ng/mL)	<0.01	<0.01	<0.01
HbA1c (3.6-6.1%)	6.70%	6.70%	6.50%
ICA	Negative	NA	Negative
IAA	Negative	NA	Negative
GADA	Negative	NA	Negative
pH(7.35-7.45)	7.02	7.41	NA
pO2 (95-115mmHg)	105.5	110	NA

pCO2 (31-44mmHg)	24.9	35	NA
Urine glucose	4+	2+	_
Urine ketone	3+	_	_
Urine Protein	_	_	_

RBC: Red blood cells; WBC: White blood cells; HB: Hemoglobin; NEUT: neutrophilia; hCRP: hypersensitive C-reactive protein; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TP: Total protein; Crea: creatinine; GADA: glutamic acid decarboxylase antibody; IAA: insulin autoantibody; ICA: islet cell autoantibody; HbA1c: glycated hemoglobin; pH: potential of hydrogen; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; .NA: NotApplicable.

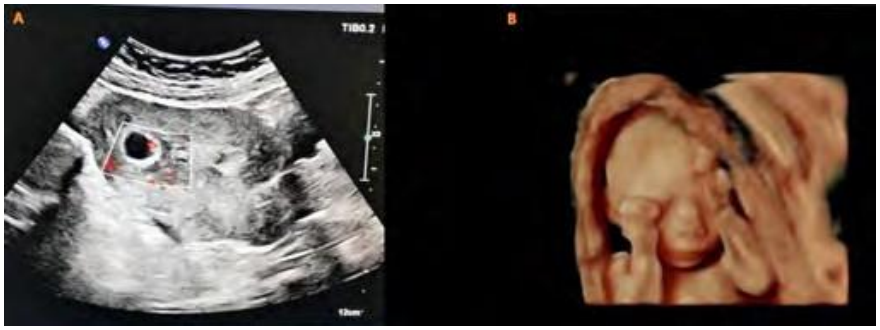

Figure1: Thefetusindifferenttrimester.

Figure1A: visiblefetal heartbeatandintrauterinelive fetusonSep 1.

Figure1B: four-dimensionalcolorultrasoundsuggestedbiparietaldiameterwas53.2mm,headcircumferencewas196mm,abdominalcircumference was 170mm, femoral length was 37. 7mm.transverse diameter of cerebellum was 21.9mm On Dec 15.

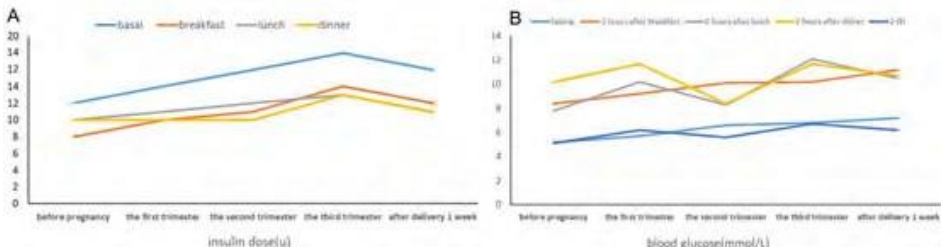

Figure2: Theinsulindoseandfluctuationofthebloodglucoseinthesecondpregnancy.

Figure2A: theinsulin dosein thesecond pregnancy.

Figure2B : thefluctuationofthebloodglucoseinthesecond pregnancy.

4. Discussion

Fulminant type 1 diabetes mellitus (FT1DM) was first reportedin2000byImagawaetal[1]. Themajorityofconfirmedcases of FT1DM occurred in East Asia, especially in Japan. In Japan, FT1DM accounts for approximately 15-20% of the ketosis-on-set or ketoacidosis-onset T1DM, and most T1DM during or af- ter pregnancy were diagnosed as FT1DM [2]. In South Korea, FT1DM accounted for 7.1% from new confirmed T1DM cases [3]. In China, The prevalence of FT1DM was 4.5% which data based from a single center [4]. In addition, a literature analysis had showed that 18% of FT1DM were related to pregnancy [5]. However, cases were sporadic in other countries. More than 90% patients with FT1DM are adults, and the incidence rate between menandwomenissimilar[2].Thecriteriafordefinitediagnosisof FT1DMwaspublishedbythecommitteeoftheJapandiabetesso- ciety,whichwere:(1)occurrenceofdiabeticketosisorketoacido- sis shortly (approximately one week) after the onset of hyperglycemicsymptoms(elevationofurinaryand/orserumketonebodies atfirstvisit),(2)plasmaglucoselevel≥16.0mmol/LandHbA1c level <8.5% at first visit, and (3) urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.10 nmol/L and <0.17 nmol/Lafterintravenousglucagon(oraftermeal)loadatonset[6].

TheetiologyandmechanismofFT1DMwasuncertain,whichmay possiblyassociatewithgeneticsusceptibility,viralinfection,pregnancy and autoimmunity [7]. It is not known why FT1DM is associatedwithpregnancy,butasweallknownthatimmunesystem ischangedduringpregnancy[8].MostT1DMduringpregnancyis FT1DM,whichmaybecorrelatedwiththechangesofimmuneenvironment [2]. Viral infection and human leukocyte antigen were also related to FT1DM [9]. Coxsackie B1 belongs to the familyof enteroviruses (EVs). Epidemiological studies have confirmeda close association between EVs and T1DM because of the EVs significantdestructionuponβ-cells,whichleadstoT1DM[10,11]. The exact pathogenesis by which EVs could causeT1DM remain unknown. HLA-DR and DQ genes were significantly correlated withtheFT1DMinpregnancy[12],unfortunately,theabovegenes were not tested.

In this case, the patient had abdominal symptoms and serum amylase above the upper laboratory limit, the increased serum pancreaticenzymelevelsdisappearedafterthetreatmentofDKA,and acutepancreatitiswasexcludedbyabdominalCTscan.Itisreported that 50% of cases with FT1DM during pregnancy had abdominalsymptomsandhigherserumlipaseand/oramylaselevels[1]. Pancreaticspecimenstakenbybiopsyshowedcellularinfiltration bothtoendocrineandexocrinepancreasinpatientswhodied1–5 days after the FT1DM, respectively [13].

Diabetes-related autoantibodies are seldom positive in FT1DM, and only 4.8% of FT1DM cases were positive for GADA, while others were negative [14]. GADA, ICA, IAAwere negative in thiscase.However,otherautoantibodies,suchasIA2,Zinctransporters, were not tested.

After the diagnosis of FT1DM, the patient became insulin-dependent, without any oral antidiabetic drugs. FT1DM decreases the chance of spontaneous pregnancy. The reason why includes the diabetic autonomic neuropathy which affecting the reproductive system; renal insufficiency which leading to an increase in prolactinaffectingovulationandsomepsychologicalfactors,etal. Compared to typical T1DM, there is no data support on fertility reduction.

In this case, the patient was diagnosed with FT1DM in her first pregnancy, the patients were treated according to the therapeutic principleofketoacidosis.AstheprognosisofFT1DMinpregnan- cy is worse than that the classic T1DM, the character of FT1DM wererapidprogress,criticalclinicalsymptoms,usuallyassociated withmultipleorgandysfunctionsuchasexocrine,liverandkidney dysfunction, and poor prognosis. We found laboratory evidenceof Coxsackie B1 virus infection. Symptoms are non-specific with virus in the early-phase, and may be easily confused with the symptomscausedbydiabetesketoacidosis.Hyperglycemia,dehydration,severeacidosis,electrolytemetabolismdisorder,hypoxia, infection,etalwereblamedforstillbirth.Thepatienthadasystematiceducationon FT1DMtomakeherhaveenoughknowledgeof thedisease.Herregularoutpatientfollow-upforfiveyearswithout complications which may lay a good foundation for the patient's second pregnancy and delivery.

T1DM complicated approximately 0.3-0.5% of pregnancies [15]. Withnocontraceptioninthepastfiveyears,thepatientconceived again in May 2021. No Pregnancy-complications, such as gestationalhypertension,fetalmacrosomia,andneonatalhypoglycemia were attributing to periodically antenatal care and blood glucose management throughout the re-pregnancy. In summary, FT1DM is a rare disease. Herein, we reported a case of successful second pregnancy and delivery five years after the diagnosis of FT1DM, withtheaimofobtainingwidespreadattentiontoFT1DMpatients, providing the patients with more consulting on their pregnancy suggestionwhichmightgetadverseoutcomesreduced.Thisreport aimingtodisplaythecasewhichandhowFT1DMpatientwas promotedthechancesofpregnancyandsuccessfully delivered.

5. EthicsStatement

Theresearchonhumanparticipantsdidnotrequireethicalreview and approval in line with the local legislation and institutional requirements. We obtained written informed consent from the patientatthetimeoftheclinicalinvestigationforthefigureanddata in this article.

6. AuthorContribution

All the authors have contributed significantly.WS collected the clinical data. GJ summarized the relevant literature. YD and WP wrote the manuscript. PD revised the manuscript. All authors agreed to submit this version.

7. DeclarationofInterest

The authors declare that they have no interests or personal relationshipsthatcouldhaveappearedtoinfluenceonthiscasereport.

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