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【 CASE REPORT 】

Fulminant Type 1 Diabetes Mellitus Presenting 15 Days after Delivery Diagnosed in Cooperation with Obstetricians

Junji Sagawa, Yoko Yoshii and Mitsunobu Kubota

Abstract:
The patient was a 32-year-old Japanese woman who was given a 75-g oral glucose tolerance test at the 35 th week of pregnancy and was normoglycemic. She had excessive thirst and polyuria from 15 days after delivery. When she visited for the 1-month postpartum checkup, her plasma glucose level was 479 mg/dL, HbA1c was 7.4%, and urinary C-peptide was 1.1 μg/mL; she was therefore diagnosed with fulminant type 1 diabetes mellitus associated with pregnancy. All physicians should be aware of this disease so as to provide a prompt diagnosis and emergency treatment and consequently improve the maternal prognosis.

Key words: type 1 diabetes mellitus, fulminant type 1 diabetes mellitus, pregnancy, delivery, diabetic ketoacidosis

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Introduction

Type 1 diabetes mellitus (T1DM) is caused by a decline in the insulin secretion function due to the disruption of pancreatic β cells, which are divided into two categories: autoimmune type (type 1A), involving an autoimmune mechanism by pancreatic islet associated autoantibody; and a spontaneous type (type 1B), in which autoimmune involvement has not been proven. Fulminant type 1 diabetes mellitus (FT1DM) is a subtype of type 1B in which the pancreatic islet cells fail rapidly, leading to hyperglycemia and ketoacidosis. FT1DM was first reported by Imagawa et al. in 2000 (1). In Japan, FT1DM accounts for about 20% of acute-onset T1DM (2). FT1DM is often related to pregnancy and can develop during pregnancy and immediately after delivery (3). The major clinical characteristics of FT1DM are a markedly abrupt onset of disease with a very short (<1 week) duration, leading to severe ketoacidosis that requires the initiation of insulin therapy.

We herein report a case of FT1DM developing immediately after delivery, in which a good outcome was achieved by close contact with the obstetrics and gynecology departments.

Case Report

The patient was a 32-year-old woman without a history of pregnancy and delivery and no family history of diabetes. She had been given a 75-g oral glucose tolerance test at the 35th week of pregnancy to rule out gestational diabetes at that time. Her fasting blood glucose was 70 mg/dL, her 1 hour post-prandial blood glucose was 88 mg/dL, and her 2 hours post-prandial blood glucose was 119 mg/dL. She was diagnosed with a normal glucose tolerance.

She delivered a girl (3,034 g, Apgar score 10 points) at 40 weeks and 6 days by natural delivery. However, 15 days after delivery, she began to have excessive thirst, polyuria, and malaise. She did not have flu-like symptoms, such as a sore throat, cough, or nasal discharge. Obstetricians realized her abnormal condition when she visited for the one-month postpartum checkup. She was emergently admitted to our hospital with symptoms of nausea, abdominal pain, and vomiting. Upon admission, the patient was 149 cm tall, weighing 38.6 kg (immediately after delivery, 45.3 kg) with a body temperature of 37.4℃, blood pressure of 123/69

Department of Endocrinology and Diabetes, National Hospital Organization KURE Medical Center, Japan
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Correspondence to Dr. Mitsunobu Kubota, takubonx@kba.biglobe.ne.jp

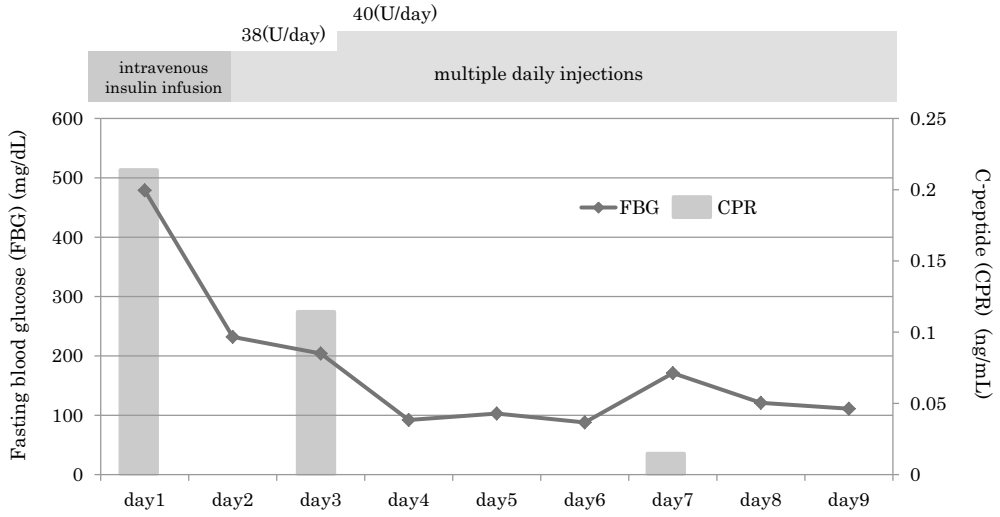
Table 1. Laboratory Data on Admissoin.

CBC		TSH	0.50 μIU/mL	Diabetes			
WBC	6,200 /μL	F-T3	1.07 pg/mL	PG	479 mg/dL		
RBC	535×10⁴ /μL	F-T4	0.91 ng/mL	CPR	0.21 ng/mL		
Hb	16.4 g/dL	Serum ketone	10,710 μmol/L	HbA1c	7.4 %		
Ht	49.3 %			GA	29.8 %		
Plt	38.1 /μL	BGA		24H U-CPR	1.1 μg/day		
Biochemistry		pH	7.162	GAD Ab	9.8 U/mL		
Na	132 mEq/L	pO_2	121 mmHg	IA-2 Ab	<0.4 U/mL		
Cl	104 mEq/L	pCO_2	15.3 mmHg	ICA	(-)		
K	4.6 mEq/L	HCO_3^-	5.2 mmol/L	Insulin Ab	<0.4 U/mL		
GOT	17 U/L	BE	-22.6 mmol/L	Glucagon			
GPT	22 U/L	Anion Gap	16.3 mmol/L	test:ΔCPR	<0.01 ng/mL		
LDH	194 U/L	Lactate	1.1 mmol/L				
γ-GTP	15 U/L			HLA serotype	DR4, DR9, DQ3		
CK	95 U/L	Coagulation		HLA genotype			
BUN	12 mg/dL	PT	11.1 s	DRB1*09:01-DQB1*03:03			
CRE	0.57 mg/dL	APTT	28.0 s	DRB1*04:03-DQB1*03:02			
T-Bil	6.0 mg/dL	FDP	<1.0 μ/mL				
TP	8.2 g/dL	D-dimer	1.1 μ/mL	Viral antibodies	on adimission	3 w after	
Alb	5.0 g/dL			CMV IgG (EIA)	4.7	4.8	
CRP	0.17 mg/dL	Urinalysis		HHV-6 IgG (FA)	80	80	
Amy	101 U/L	pH	5.5	EBV IgG (ELISA)	2.6	2.8	
Lipase	59 IU/L	protein	(2+)	Coxackei A4	<4	<4	
Elastase-1	73 ng/dL	glucose	(4+)	Coxackei A5	<4	<4	
T-Cho	247 mg/dL	blood	(3+)	Coxackei A6	<4	<4	
HDL-Cho	55 mg/dL	ketone	(3+)	Coxackei B1	<4	<4	
TG	126 mg/dL			Coxackei B4	<4	<4	

CBC: complete blood count, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet count, GOT: glutamic oxaloacetic transaminase, GPT: glutamic pyruvic transaminase, LDH: lactate dehydrogenase, γ-GTP: gamma-glutamyl transpeptidase, CK: creatine kinase, BUN: blood urea nitrogen, CRE: creatine, T-Bil: total bilirubin, TP: total protein, Alb: albumin, CRP: C-reactive protein, Amy: amylase, T-Cho: total cholesterol. HDL-Cho: high-density lipoprotein cholesterol, TG: triglyceride, TSH: thyroid-stimulating hormone, BGA: blood gas analysis, BE: base excess, PG: plasma glucose, CPR: C-peptide immunoreactivity, GA: glycoalbumin, 24H U-CPR: 24hours urinary C-peptide immunoreactivity, GAD Ab: antibody against glutamic acid decarboxylase, IA-2 Ab: anti-insulinoma-associated antigen-2 antibody, ICA: islet cell antibody, Insulin Ab: insulin antibody, Glucagon test: Δ CPR: the amount of increased serum C-peptide in a glucagon stimulation test, HLA: human leukocyte antigen, CMV: cytomegalovirus, EIA: enzyme immunoassay, HHV: human herpesvirus, FA: fluorescent antibody method, EBV: Epstein-Barr virus, ELISA: enzyme-linked immunosorbent assay

mmHg, and a respiration rate of 12 times/min. A physical examination revealed spontaneous pain and tenderness in the upper abdomen. As shown in Table 1, she developed diabetic ketoacidosis (DKA), with a random sample glucose of 479 mg/dL, arterial pH of 7.162, PaO_2 of 121 mmHg, $PaCO_2$ of 15.3 mmHg, BE of -22.6 mmol/L, HCO_3^- of 5.2 mmol/L, lactate of 1.1 mmol/L, anion gap of 16.3 mmol/L, 3+ urinary ketone bodies, and serum ketone of 10,710 μg/mL. Despite the presence of DKA, the HbA1c value was 7.4%, which was relatively low compared to the blood sugar level. In addition, the serum lipase level was slightly increased to 73 IU/L, but neither amylase nor elastase-1 levels were within the normal range. The plasma C-peptide (CPR) level progressively decreased day by day: 0.11 ng/mL on day 2, and <0.03 ng/mL on day 7. In a glucagon stimulation test, the ΔCPR was <0.01 ng/mL, and the urinary CPR was 1.1 μg/day. Antibody against glutamic acid decarboxylase (GADAb) was 9.8 (<5.0) U/mL. Neither islet cell antibody (ICA) nor anti-insulinoma-associated antigen-2 (IA-2Ab) antibodies were detected. Human leukocyte antigen (HLA) class II haplotypes were DRB1*09:01-DQB1*03:03 and DRB1*04:03-DQB1*03:02. Paired serum examinations for viral infections, such as Coxsackie, human herpesvirus 6 (HHV-6), and Epstein-Barr virus (EBV), which are known to be associated with the development of FT1DM, showed no clear evidence of a viral infection. The thyroid function was normal, and anti-thyroid autoantibody group was negative.

With a diagnosis of FT1DM, the patient was treated with intravenous insulin infusion. With the improvement of her ketoacidosis, her symptoms, such as upper abdominal pain, nausea, and malaise, also improved. After confirming that HCO_3^- was almost normalized by a blood gas analysis, she started oral ingestion and shifted to multiple daily injections with insulin lispro and degludec (Figure). Thereafter, her plasma glucose level was satisfactorily controlled, and she was discharged.



pH	7.162	7.335
pO_2(mmHg)	121	101.7
pCO_2(mmHg)	15.3	30.0
HCO_3^-(mmol/L)	5.2	15.6

Figure. **The clinical course of this case. Multiple daily injections were started after intravenous insulin infusion. The plasma glucose level was controlled satisfactorily, and she was discharged.**

Table 2. **Criteria for Definite Diagnosis of Fulminant Type 1 Diabetes Mellitus (2012)(3).**

Fulminant type 1 diabetes mellitus is confirmed when all the following three findings are present:

1) Occurrence of diabetic ketosis or ketoacidosis soon (approximately 7 days) after the onset of hyperglycemic symptoms (elevation of urinary and/or serum ketone bodies at first visit)

2) Plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) and glycated hemoglobin level <8.7% (NGSP value)† at first visit

3) Urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/mL (<0.10 nmol/L) and <0.5 ng/mL (<0.17 nmol/L) after intravenous glucagon (or after meal) load at onset

Other findings in fulminant type 1 diabetes mellitus

A) Islet-related autoantibodies, such as antibodies to glutamic acid decarboxylase, islet-associated antigen 2 and insulin, are undetectable in general

B) Duration of the disease before the start of insulin treatment can be 1-2 weeks

C) Elevation of serum pancreatic enzyme levels (amylase, lipase or elastase-1) is observed in 98% of the patients

D) Flu-like symptoms (fever, upper respiratory symptoms, etc.) or gastrointestinal symptoms (upper abdominal pain, nausea and/or vomiting, etc.) precede the disease onset in 70% of patients

E) The disease can occur during pregnancy or just after delivery

F) Association with HLA DRB1*04:05-DQB1*04:01 is reported

† This value is not applicable for patients with previously diagnosed glucose intolerance.

HLA: human leukocyte antigen, NGSP: National Glycohemoglobin Standardization Program

Discussion

According to the diagnostic criteria for FT1DM published from The Japan Diabetes Society (Table 2) (3), this case was diagnosed with FT1DM by satisfying three of the diagnostic criteria. It has been reported that FT1DM is more likely to develop during pregnancy and immediately after delivery (3). Almost all patients who develop T1DM during pregnancy or immediately after delivery have FT1DM, accounting for 22.7% of all FT1DM cases developing in women of childbearing age (13-49 years), and the disease generally manifests late in pregnancy (4). The present patient developed FT1DM 15 days after parturition but was diagnosed with FT1DM associated with pregnancy (PF) based on the clinical course. FT1DM that develops during pregnancy or immediately after delivery (<2 weeks) is referred to as PF (5). It is suggested that pancreatic β cells are destroyed rapidly, resulting in the rapid depletion of endogenous insulin secretion in cases of PF. Our present patient had undergone a 75-g oral glucose tolerance test at the 35th week of pregnancy (45 days before FT1DM onset), which confirmed that her glucose tolerance was normal at that time. In addition, the rapid progressive depletion of endogenous insulin secretion (the plasma CPR level was 0.11 ng/mL on day 2, and <0.03 ng/mL on day 7) was observed. In

Table 3. Clinical Characteristics of Eight PF Cases That Developed after Delivery.

Age (years)	Onset day after delivery (days)	Duration (days)	Weight of newborn (g)	Serum glucose (mg/dL)	HbA1c (%)	Serum C-peptide (ng/mL)	Urinary C-peptide (mg/day)	Amylase (IU/L)	Lipase (U/L)	Elastase-1 (ng/dL)	Arterial pH	Auto-antibody			HLA serotype	HLA genotype	Reference No.
												GAD	IA-2	ICA			
32	3	3	3,072	1,350	8.7	0.2	2		104	490	7.01	ND	ND	-	DR 9/12	ND	(6)
33	14	4	3,212	1,414	7.9	<0.1	8.8	372	90	ND	7.03	-	ND	-	DR 4/8, DQ 1/4	ND	(7)
33	13	2	ND	1,196	6.7	0.2	1.6	44	ND	ND	7.12	-	-	-	DR 4/-, DQ 4 /-	DRB1*0405/0405	(8)
26	11	3	2,924	725	6.9	ND	4	434	118	ND	7.17	-	-	-	DE 4/10, DQ 4/5	DRB1*04:05-DQB1*04:01 DRB1*10:01-DQB1*05:01	(9)
29	7	1	2,888	835	7.1	0.15	1.6	142	130	470	7.1	-	-	-	DR 6/11, DQ 1/3	ND	(10)
36	2	1	1,100	649	6.4	ND	17.7	high	ND	ND	7.12	-	-	-	DR 4, DQ 3/4	ND	(11)
25	11	2	3,948	1,030	6	0.02	0.1	136	171	2,690	7.04	-	-	-	DR 4/15, DQ 3/5	DRB1*04:10-DQB1*03:02 DRB1*15:02-DQB1*05:01	(12)
32	15	7	3,034	479	7.4	0.01	1.1	101	73	206	7.162	+†	-	-	DR 4/9, DQ3	DRB1*09:01-DQB1*03:03 DRB1*04:03-DQB1*03:02	Our case

†The GADab levels decreased to <5.0 U/mL one month after onset.
Duration shows the period of hyperglycemic symptoms before the diagnosis of the diabetes.
ND: not described

our review of the literature, there were eight cases of PF that developed after delivery in Japan (Table 3) (6-12). Compared to the previous cases, the duration of hyperglycemic symptoms before the diagnosis was longer and the levels of serum and urinary CPR much lower in the present case.

Although the detailed mechanisms underlying the occurrence of FT1DM in relation to pregnancy have not yet been clarified, HLA and viral infection are considered to be involved. HLA class II genotypes are estimated to account for 50% of all cases of acute-onset T1DM (13, 14). Similarly, a HLA class II genotype strongly sensitizes the development of FT1DM (4, 15, 16). HLA class II haplotypes contribute to the development of PF or FT1DM that is not associated with pregnancy (NPF), although the relevant HLA class II haplotypes appear to differ between PF and NPF (4, 15). FT 1DM has been reported to be associated with DRB1*04:05-DQB1*04:01 in Japan (17). DRB1*04:05-DQB1*04:01 is significantly more frequent in NPF than in PF, while DRB1 *0901-DQB1*0303 is significantly more frequent in PF than NPF (18). The involvement of HLA class II haplotypes is suggested to vary depending on the presence or absence of pregnancy. In the present patient, the HLA II haplotypes were DRB1*09:01-DQB1*03:03 and DRB1*04:03-DQB1* 03:02. Thus, this patient had a genetic background that made her susceptible to developing PF.

Because FT1DM often precedes flu-like symptoms, the involvement of a virus infection has been suggested (2, 5). However, our patient did not have any flu-like symptoms, and no significant increase in viral antibody was observed. In response to a viral infection, antigen-presenting cells, such as dendritic cells and macrophages, activate T cells via Toll-like receptor 3/4 (TLR 3/4). At the same time, inflammatory cytokines, such as interferon, are produced by the infection and delivered to pancreatic β cells. However, Regulatory T cells (Tregs), as a defense system against cytotoxic T cells, suppress the effect of cytotoxic T cell and Tregs have an effect which prevents destruction of β cells by cytotoxic T cells; therefore, if Tregs are sufficiently active to suppress cytotoxic T cell activity, the onset of FT1 DM is suppressed. The number of Tregs varies during pregnancy (19); Somerset et al. reported that the number increases from early pregnancy and decreases after reaching a peak in the middle of pregnancy. After the end of pregnancy, cytotoxic T cells are more likely to be activated by virus infection because the number of Tregs decrease from the late pregnancy stage, and this makes β cells more susceptible to damage by cytotoxic T cells, in other words, the normal defense mechanism may deteriorate, thus leading to the onset of FT1DM. In addition, interleukin-21 (IL-21), which induces immunoglobulin production from B cells, is produced from follicular helper T cells and is reported to be associated with autoimmune T1DM (20). The IL-21 level was found to be significantly lower in the third trimester of pregnancy than in non-pregnant women (21), which may be related to FT1DM being more likely to develop during preg-

nancy and immediately after delivery than autoimmune type 1 diabetes.

In conclusion, no significant differences in the age of onset, BMI, family history, disease duration, CPR, or GADAb were noted between PF and NPF, but the arterial blood pH of PF was significantly lower than that of NPF (18); therefore, PF may have a poorer prognosis than NPF, even after delivery. This case had extremely low arterial blood pH; as such, if the diagnosis had been delayed, the patient might have died. All medical professionals, including obstetricians, must recognize that FT1DM is likely to develop during pregnancy or immediately after delivery. If a pregnant woman or a woman immediately after delivery suddenly develops hyperglycemic symptoms, such as thirst, polydipsia, or polyuria, it is necessary to bear in mind the possibility of FT1DM.

The authors state that they have no Conflict of Interest (COI).

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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 **342**: 301-307, 2000.

2. Imagawa A, Hanafusa T, Uchigata Y, et al. Fulminant type 1 diabetes:a nationwide survey in Japan. Diabetes Care **26**: 2345-2352, 2003.

3. Imagawa A, Hanafusa T, Awata T, 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). J Diabetes Investig **3**: 536-539, 2012.

4. Tsutsumi C, Imagawa A, Ikegami H, et al. Class II HLA genotype in fulminant type 1 diabetes: a nationwide survey with reference to glutamic acid decarboxylase antibodies. J Diabetes Investig **3**: 62-69, 2012.

5. Shimizu I, Makino H, Osawa H, et al. Association of fulminant type 1 diabetes with pregnancy. Diabetes Res Clin Pract **62**: 33-38, 2003.

6. Ichiki Y, Nagamine N, Tsuruta H, Tamura K, Yokota T, Seita M. A case of IDDM presented with post-partum diabetic ketoacidosis. Tounyoubyou To Taisha (Diabetes J) **18**: 155-159, 1990 (in Japanese).

7. Seino H, Watanabe Y, Yamazaki T, Atami M, Kikuchi H, Abe R. Bunnbenngo tounyoubyousei ketoacidosis nite hasshou sita insulin izonnsei tounyoubyou no ichirei. Tounyoubyou (J Japan Diabetes Soc) **42**: 447-450, 1999 (in Japanese).

8. Misaki A, Kotani T, Seino H, et al. Non-autoimmune fulminant typel diabetes mellitus presenting with diabetic ketoacidosis after the delivery. Nihon Naika Gakkai Zasshi (J Jpn Soc Intern Med) **92**: 659-661, 2003 (in Japanese).

9. Shimizu I, Fujii Y, Kohnoue E, et al. Five suspected cases of nonautoimmune fulminant type 1 Diabetes mellitus. Tounyoubyou (J Japan Diabetes Soc) **44**: 315-322, 2001 (in Japanese, Abstract in English).

10. Hayakawa N, Makino M, Kakizawa H, et al. A case of fulminant type 1 diabetes mellitus acquired in the 7th week of pregnancy. Tounyoubyou (J Japan Diabetes Soc) **45**: 325-328, 2002 (in Japanese, Abstract in English).

11. Inagaki T, Nishii Y, Suzuki N, et al. Fulminant diabetes mellitus associated with pregnancy: case reports and literature review. Endocr J **49**: 319-322, 2002.

12. Furukawa S, Fujihara K, Kumagai R, et al. Fulminant type 1 diabetes mellitus presenting 11 days after delivery in a patient of mixed genetic background. Intern Med **55**: 1881-1885, 2016.

13. Inagaki T, Nishii Y, Suzuki N, et al. Fulminant diabetes mellitus associated with pregnancy: case reports and literature review. Endocr J **49**: 319-322, 2002.

14. Davies JL, Kawaguchi Y, Bennett ST, et al. A genome-wide search for human type 1 diabetes susceptibility genes. Nature **371**: 130-136, 1994.

15. Shimizu I, Makino H, Imagawa A, et al. Clinical and immunogenetic characteristics of fulminant type 1 diabetes associated with pregnancy. J Clin Endocrinol Metab **91**: 471-476, 2006.

16. Tanaka S, Kobayashi T, Nakanishi K, et al. Association of HLADQ genotype in autoantibody-negative and rapid-onset type 1 diabetes. Diabetes Care **25**: 2302-2307, 2002.

17. Imagawa A, Hanafusa T, Uchigata Y, et al. Different contribution of class II HLA in fulminant and typical autoimmune type 1 diabetes mellitus. Diabetologia **48**: 294-300, 2005. Erratum in Diabetologia **51**: 524-526, 2008.

18. Shimizu I, Makino H, Imagawa A, et al. Clinical and immunogenetic characterisitics of fulminant thpe 1 diabetes associated with pregnancy. J Clin Endocrinol Metab **91**: 471-476, 2006.

19. Somerset DA, Zheng Y, Kilby MD, et al. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-Cell subset. Immunology **112**: 38-43, 2004.

20. Ferreira RC, Simons HZ, Thompson WS, et al. IL-21 production by CD4+ effector T cells and frequency of circulating follicular helper T cells are increased in type 1 diabetes patients. Diabetologia **58**: 781-790, 2015.

21. Poordast T, Najib FS, Baharlou R, et al. Assessment of T helper 17-associated cytokines in third trimester of pregnancy. Iran J Immunol **14**: 172-179, 2017.