Factor X Deficiency Management for Elective Cesarean Delivery in a Pregnant Patient

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Source / Izvornik: **American Journal of Case Reports, 2020, 21**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.12659/AJCR.920685

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:632021

American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e920685
DOI: 10.12659/AJCR.920685

Received: 2019.10.14
Accepted: 2020.01.25
Available online: 2020.02.06
Published: 2020.03.18

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Conflict of interest: None declared

Patient: Female, 39-year-old
Final Diagnosis: Factor X deficiency
Symptoms: Menstrual bleeding
Medication: Solvent-detergent-treated fresh frozen plasma
Clinical Procedure: Elective cesarean section
Specialty: Obstetrics and Gynecology

Objective: Rare co-existance of disease or pathology

Background: Congenital factor X deficiency is a rare inherited coagulopathy. Pregnancies in women with this disorder are often associated with adverse outcomes, including miscarriage, premature labor, and hemorrhage during pregnancy and in the peripartum period. The literature on this disorder is sparse and shows a limited number of successful pregnancies in women with factor X deficiency.

Case Report: In this report, we present the case of a successful pregnancy and term delivery by elective cesarean section in a 39-year-old primigravida with congenital factor X deficiency. Medical management followed the recommendations of an interdisciplinary team comprising specialists in obstetrics, anesthesia, transfusion medicine, hematology, and neonatology. This high-risk pregnancy was successfully brought to term, and a healthy male neonate was delivered by elective cesarean section at 39 weeks' gestation. The patient's factor X deficiency (0.19 kIU/L) was treated using 4 units of solvent-detergent-treated fresh frozen plasma (SD-FFP) 1 h before the cesarean section, leading to hemostatic levels of factor X and an uneventful intraoperative course. Postoperatively, the patient's factor X levels were controlled daily and corrected using SD-FFP as needed, with no clinically significant blood loss.

Conclusions: SD-FFP can be used to manage congenital factor X deficiency in the peripartum period and maintain perioperative blood loss within normal limits.

MeSH Keywords: Factor X Deficiency • Pregnancy Complications, Hematologic • Pregnancy, High-Risk

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/920685

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Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Factor X is a vitamin K-dependent serum protease synthesized in the liver [1,2]. It is the first coagulation factor of the common pathway; once activated, it catalyzes the conversion of prothrombin to thrombin [1]. Congenital factor X deficiency is a rare coagulation disorder with an incidence of 1: 1 000 000 [3,4]. The condition is inherited in an autosomal recessive fashion, with homozygous individuals usually showing a pronounced bleeding disorder. In heterozygotes, symptoms can range from no bleeding diathesis to severe hemorrhage in situations that involve hemostatic challenge, such as surgery or tissue trauma [1,4,5]. Although the level of factor X deficiency is not always directly correlated with bleeding disorder severity, lower factor X levels generally confer a higher risk for hemorrhagic complications [4,5].

Menstruation, pregnancy, and childbirth make women with factor X deficiency more susceptible to clinically significant bleeding. In healthy women, factor X progressively increases during normal pregnancy [6]. Starting from a normal value between 50% and 150%, levels rise at 12–30 weeks' gestation, peaking at an average value of 163% [6]. A second rise occurs 144 h postpartum, when levels can reach 173%. After this secondary peak, levels decrease to preconception values within 6 weeks [6]. This physiological rise in factor X usually also occurs in women with mild-to-moderate factor X deficiency, and rarely in women with severe factor X deficiency.

The relationship between coagulation factors and normal physiological changes in pregnancy is complex, and factor X deficiency has been associated with adverse pregnancy outcomes, including miscarriage, premature labor, and hemorrhage during pregnancy or in the peripartum period [3,5]. According to Spiliopoulus et al., between 1960 and 2018 there were 31 reported pregnancies in 19 women with factor X deficiency [4]. Four of these 31 (13%) resulted in miscarriage, 4/31 (13%) were associated with vaginal bleeding during pregnancy, 6/31 (22%) led to postpartum hemorrhage, and 8 of the successful pregnancies (8/27; 30%) involved preterm delivery (<37 weeks) [4].

In the present report, we present a successful pregnancy and term delivery by elective cesarean section in a 39-year-old primigravida with congenital factor X deficiency whose peripartum factor X levels were increased using solvent-detergent-treated fresh frozen plasma (SD-FFP).

Case Report

A 39-year-old nulliparous woman was referred to our tertiary care center because she had a known history of factor X deficiency. Her coagulation disorder was diagnosed at the age of 18 years during a routine preoperative assessment for an elective tonsillectomy. Once discovered, the elective surgery was postponed and molecular diagnostics were performed. These showed that the patient was heterozygous for 2 mutations: *MTHFR C677T* and *PAI-1 4G/5G*. Subsequently, other family members were also tested, and it was found that both the patient's sister and nephew were heterozygous for the same mutations; all of these patients had factor X levels of 0.5 kIU/L and were therefore diagnosed with mild factor X deficiency.

When asked about her medical history prior to diagnosis of factor X deficiency, the patient reported reoccurring heavy menstrual bleeding, without increased incidence of other signs and symptoms related to her factor X deficiency (i.e., epistaxis, petechiae, hematoma formation, and bruising) and denied other chronic comorbidities. Moreover, no additional bleeding, apart from reoccurring heavy menstrual bleeding, was noticed between the time of diagnosis and the following medical procedures.

At the age of 37 years, the patient underwent a tooth extraction, which was monitored by a transfusion specialist. During that procedure, her coagulation test showed a prothrombin time (PT) of 0.51, an international normalized ratio (INR) of 1.4, an activated thromboplastin time (aPTT) of 37.06 s, and a factor X level of 0.25 kIU/L, which prompted the transfusion specialist to recommend administering 10 mL/kg of FFP before the procedure. The procedure was then carried out under local anesthesia. No intra- or post-operative complications were reported, and the patient was discharged from the hospital the following day.

At the age of 38 years, the patient experienced her first pregnancy, which ended in miscarriage at 8 weeks. Due to heavy vaginal bleeding and lack of fetal cardiac activity, medical abortion was performed with 400 mg of misoprostol (Stada, VietNam-Singapore Industrial Park, Binh Duong, Singapore), administered buccally. No bleeding complications were reported and the clinical course did not require administration of FFP or coagulation factors.

The patient's second pregnancy occurred at the age of 39 years and was closely monitored by the obstetrician and hematologists with regular follow-up appointments. No bleeding complications occurred during the pregnancy. However, polyhydramnion and gestational diabetes developed, with the latter being well controlled with an appropriate diet. During the third trimester, a multidisciplinary team comprising specialists in obstetrics, anesthesia, transfusion medicine, hematology, and neonatology met and devised a thorough plan for safe delivery and postpartum period. The plan included scheduled admission to the hospital at 39 weeks, daily assessments of factor X levels with therapy adjusted accordingly, and term delivery of the high-risk pregnancy by elective cesarean section.

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Table 1. Laboratory test results.

Haematology tests	Reference range (Sex: F)	Admission	Postoperative day: 5th
Erythrocytes (×10^{12}/L)	3.86–5.08	4.55	3.99
Haemoglobin (g/L)	119–157	143	123
Haematocrit (cb,vb) (L/L)	0.356–0.470	0.431	0.372
MCV (fL)	83.0–97.2	94.9	93.3
MCH (pg)	27.4–33.9	31.4	30.9
MCHC (gL)	320–345	331	331
RDW (%)	9.0–15.0	13.4	13.4
HDW (g/L)	22.0–32.0	26.6	
Thrombocytes (×10^{9}/L)	158–424	171	**140 L**
MPV (fL)	6.8–10.4	9.7	10.0
Leukocytes (×10^{9}/L)	3.4–9.7	**11.1 H**	**12.6 H**
Neutrophil granulocytes (×10^{9}/L)	2.06–6.49	**8.40 H**	**10.6 H**
Lymphocytes (×10^{9}/L)	1.19–3.35	1.80	1.20
Monocytes (×10^{9}/L)	0.12–0.84	0.50	0.60
Eozinophil Granulocytes (×10^{9}/L)	0–0.43	0.10	0.00
Basophil Granulocytes (×10^{9}/L)	0–0.06	0.00	0.00
LUC (x109/L)	0–0.40	0.20	
Neutrophil Granulocytes (rel%)	44–72	**75.9 H**	**84.6 H**
Lymphocytes (rel%)	20–46	**15.9 L**	**9.9 L**
Monocytes (rel%)	2–12	4.8	5.0
Eozinophil Granulocytes (rel%)	0–7	0.8	0.1
Basophil Granulocytes (rel%)	0–1	0.4	0.4
LUC (rel%)	0–4	2.2	
Haematology tests	**Reference range (Sex: F)**	**Admission**	**Postoperative**
Percentage of hypochromic red cells (% HYPO) (%)	0–2.5	1	
Segment indeks	1.90–3.00	2.40	
Biochemical analysis	**Reference range (Sex: F)**	**Admission**	**Postoperative**
Glucose (s) (mmol/L)	4.4–6.4	4.6	
Urea (s) (mmol/L)	2.8–8.3	**2.0 L**	
Creatinine (s) (mmol/L)	49–90	**45 L**	
eGFR CKD-EPI (mL/min/1.73 m^{3})	>90	122	
Sodium (Na) (s) (mmol/L)	137–146	139	
Potassium (K) (s) (mmol/L)	3.9–5.1	4.3	
Chlorides (s) (mmol/L)	97–108	104	

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Table 1 continued. Laboratory test results.

Urinalysis	Reference range (Sex: F)	Admission
Chemical examination		
Specific gravity (kg/L)	1.002–1.030	1.020
pH	5.0–9.0	6.0
Leukocyte esterase (/)	Neg	Neg
Protein (/)	Neg	Neg
Glucose (/)	Norm	Norm
Ketones (/)	Neg	**Pos [+]**
Urobilinogen (/)	Norm	Norm
Bilirubin (/)	Neg	Neg
Nitrites (/)	Neg	Neg
Erythrocytes/Haemoglobin (/)	Neg	Neg
Microscopic examination		
Sediment		Low RBC and LBC content, an increased number of epithelial cells and crystals Ca-oxylates are present,and few bacterias
Visual examination		
Urine clarity (/)	Clear	Slightly cloudy
Urine color (/)	Pale yellow	Yellow

As scheduled, the patient was admitted to the hospital at 39 weeks, weighing 90 kg and with BMI of 32 kg/m^2. At that time, the first set of laboratory investigations was made (Table 1, time point: admission). The patient's coagulation parameters included a prothrombin time of 0.48, an INR of 1.45, an activated thromboplastin time of 36.5 s, and a factor X level of 0.19 kIU/L. Her levels of fibrinogen, factor II, and factor VII were slightly elevated, and thrombelastography showed values within the normal range (Table 2, time point: admission).

Based on the patient's factor X levels, risk of bleeding during obstetric procedures, and the fact that heavy bleeding cannot be fully predicted in cases like this, we decided that she should receive 4 units of SD-FFP 1 h before the elective cesarean section. Two other therapeutic options were discussed: application of recombinant factor X or prothrombin complex concentrate (PCC). Although recombinant factor X would have been our first choice, it is, unfortunately, not available in our country. On the other hand, we decided against PCC due to its possible thrombogenic effect, which is especially pronounced in pregnancy. Administration of SD-FFP resulted in factor X levels of 0.41 kIU/L at the time of the procedure (Table 2, time point: preoperative). In addition, 2 units of packed red blood cells and 6 units of SD-FFP were placed on standby in case she developed bleeding complications during the procedure.

Because the patient had hemorrhagic diathesis, neuraxial anesthesia might have led to complications. For this reason, the patient was given general anesthesia. Propofol (MCT Fresenius, Bad Homburg, Germany) and rocuronium (MSD, Kenilworth, NJ, USA) were administered intravenously, followed by anesthesia and rapid-sequence intubation. Sevoflurane (AbbVieNorth Chicago, IL, USA) was then used to maintain anesthesia, and the obstetricians proceeded with the delivery. Several minutes later, a healthy baby boy was delivered, with an Apgar score of 7/9 and a weight of 3450 g. After the baby was delivered, the anesthesia was augmented with i.v. sufentanil (Hameln, Germany). Intraoperatively, the patient received 15 IU of i.v. oxytocin (Syntocinon; Mylan, Canonsburg, PA, USA), 0.2 mg of i.v. methylergometrine (Demergin; Demo, Germany), and 800 mg of misoprostol (Stada, VietNam-Singapore Industrial Park, Binh Duong, Singapore), administered rectally. The rest of the procedure was performed as planned, with no bleeding complications and no need to administer additional blood products.

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Table 2. Coagulation tests results.

Tests	Reference range	January 2019	Admission	Preoperative	Postoperative day				
					1st	2nd	3rd	4th	5th
Prothrombin time (1)	0.70–1.40	**0.45 L**	**0.48 L**	**0.62 L**	**0.64 L**	**0.62 H**	**0.65 H**	**0.66 L**	**0.63 L**
Prothrombin time – INR (INR)		1.50	1.45	1.27	1.24	1.27	1.24	1.23	1.26
Activated partial thromboplastine time (s)	25.00–40.00	32.95	36.51	32.38	32.72	36.52	37.79	35.83	38.14
Activ. partial thromboplastine time – R (1)	0.80–1.20	1.01	1.12	1.00	1.01	1.12	1.16	1.10	1.17
Fibrinogen (g/L)	1.80–4.00	**6.58 H**	**5.94 H**	**5.59 H**	**5.69 H**	**5.65 H**	**6.2 H**	**5.75 H**	**5.27 H**
D-dimeri Innovance (FEU) (mg/L)	<0.50					**2.69 H**	**1.58 H**	**1.69 H**	**1.52 H**
Antithrombin III (1)	0.75–1.25	0.97	1.03		0.94	0.96	0.99	1.0	1.0
F II Prothrombin (kIU/L)	0.70–1.20	**1.75 H**	**1.46 H**						
F V Proaccelerin (kIU/L)	0.70–1.40	1.27	1.12						
F VII Proconvertin (kIU/L)	0.70–1.20	**1.99 H**	**1.83 H**						
F X Stuart-Power (kIU/L)	0.70–1.20	**0.22 L**	**0.19 L**	**0.41 L**	**0.30 L**	**0.27 L**	**0.32 L**	**0.34 L**	**0.33 L**
Thromboelastogram-R [min]	4.00–8.00	6.80	5.80						
Thromboelastogram-K [min]	0.00–4.00	1.80	1.30						
Thromboelastogram-alpha [o]	47.00–74.00	65.00	70.80						
Thromboelastogram-MA [mm]	54.00–72.00	68.00	**72.40 H**						
Thromboelastogram-CL [1/1]	-3.00–3.00	0.40	2.22						

After an uneventful stay in the postoperative care unit, the patient was discharged to the high-dependency unit (HDU) of the Department of Gynecology and Obstetrics. Over the next 5 days, her factor X levels were assessed regularly (Table 2, time point: postoperative days 1–5), and SD-FFP was administered as needed. Post-operatively, the patient received a total of 15 units of SD-FFP, with no significant blood loss. She and her healthy son were discharged from the hospital on day 7, with subsequent ambulatory follow-ups.

Discussion

The perioperative blood management approach used by our multidisciplinary team resulted in a successful term delivery and uneventful peripartum period in a patient with factor X deficiency, without significant bleeding or thrombotic complications.

Factor X deficiency is a rare inherited coagulopathy, manifested as various degrees of bleeding diathesis [3]. The amount of factor X required to accomplish hemostasis is unknown, but levels of 10–35% are thought to be sufficient [7]. In severe cases of factor X deficiency, bleeding complications can arise in the neonatal period in the form of intracranial hemorrhage or umbilical cord stump hemorrhage (usually 1–2 weeks after birth, when the stump dries and falls off) [7]. Less severe cases of factor X deficiency can result in bleeding complications in situations involving hemostatic challenge, such as surgery, tissue trauma, and menstrual cycle [7]. Irrespective of the level of factor X, the most commonly reported symptom in factor X-deficient patients is epistaxis, which was reported to occur in 72% of patients [7]. Regarding laboratory investigations, in standard coagulation tests consisting of PT, INR, aPTT, fibrinogen concentration, and platelet count, patients with factor X deficiency usually have prolonged PT, INR, and aPTT [7]. However, to make a definite diagnosis, a functional assay for factor X has to be performed, with optional molecular genetic testing for variation in the factor X gene [7].

As previously mentioned, factor X-deficient women are more prone to clinically significant bleeding due to specific physiological changes during their reproductive years [4]. It also appears that factor X deficiency can be linked to a higher risk of adverse pregnancy outcomes. Factor X-deficient women have a higher risk of miscarriage, premature labor, and hemorrhage during pregnancy or in the peripartum, with the most extreme

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cases ending with massive hemorrhage necessitating hysterectomy [4]. Moreover, data show a greater incidence of preterm birth and neonatal death in pregnancies that reached the stage of fetal viability [4]. In summary, women with factor X deficiency have a higher risk for greater hemorrhage during their menstrual cycle, unfavorable pregnancy outcomes, and peripartum bleeding [4].

The first case of a pregnant woman with factor X deficiency was reported by Brody et al. in 1960 [8]. Konje et al. commented on a young woman with this coagulopathy who developed retroplacental hematomas during pregnancy. During her hospitalization, she was treated with Bioproduct Laboratory factor X and there were no complications during her delivery by a cesarean section [9]. Kumar and Mehta described a factor X-deficient woman during her 4 pregnancies who was treated with prophylactic substitute of coagulation factors. Her pregnancy and delivery ended with a positive outcome with no postpartum complications [10]. Bofill et al. described a factor X-deficient patient in her early twenties who did not receive replenishment with coagulation factors, and the decision was made to treat her with FFP while she was in labor and during the first day after giving birth to her child; there was no significant blood loss and she delivered a healthy newborn [11]. The present case management was similar to that reported by Venkatesh et al., in which a young patient with severe factor X deficiency underwent emergency cesarean section after a retroplacental bleed of approximately 50 mL was observed by ultrasound [7]. The patient was at 37 weeks of gestation and was treated with FFP and i.v. tranexamic acid preoperatively and in the early postoperative period after a healthy baby boy was delivered [7]. In the present case, an elective cesarean section was planned at 39 weeks' gestation. Because the patient had low levels of factor X (0.19 kIU/L), she was scheduled to receive 4 units of SD-FFP 1 h before the cesarean section to elevate her levels of factor X above 50%. In the postoperative period (during the next 3 days), she received 15 units of SD-FFP. During the operation and in the postoperative period, her blood loss was within normal limits (see Table 1, time point: postoperative). She was discharged from the hospital after 7 days with a healthy baby boy.

Due to limited reported data, there is no agreement regarding the recommendation for antenatal prophylaxis in all pregnant women with factor X deficiency. Each pregnant woman with factor X deficiency has a unique clinical course and should be managed and treated individually. Antenatal prophylaxis should be well planned in each pregnancy with severe deficiency, particularly for cases with obstetric complications or bleeding during pregnancy. The hemostatic strategy during delivery should be planned individually considering the level of factor X, maternal loss of blood, and the obstetric possibility of bleeding [4].

The American Society of Anesthesiologists Task Force on Perioperative Blood Management states that FFP is indicated for correction of excessive microvascular bleeding (i.e., coagulopathy) in the presence of an INR greater than 2.0 or for correction of excessive microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than 1 unit of blood volume (approximately 70 ml/kg) and when PT, INR, or PTT cannot be obtained in a timely fashion [12].

Conclusions

The present case involved a woman with severe factor X deficiency who was scheduled for a planned cesarean section. To optimize outcome and minimize the patient's risk for hemorrhage, a multidisciplinary approach was used: factor X levels were monitored during pregnancy, as well as in the preoperative and early postoperative period, a predefined labor plan was devised, and intraoperative and early postoperative SD-FFP was used.

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