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MEDICINE

Factor VII Deficiency and Pregnancy: Case Report and Review of Literature

Minakshi Rohilla[1] · Rakhi Rai[1] · Jasmina Ahluwalia[2] · Pankaj Malhotra[3] · Vanita Jain[1]

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Abstract

Inherited Factor VII deficiency is an autosomal recessive coagulation disorder with broad range of bleeding manifestations. The association between bleeding and absolute Factor VII level is poor. Usually, the bleeding is associated with FVII levels of less than 1% of the normal value. Factor VII deficiency is associated with prolongation of prothrombin time only with normal activated partial thromboplastin time. Very few pregnant women have been reported with Factor VII deficiency so far in English literature. We, hereby, report 2 cases along with the review of literature of Factor VII deficiency during pregnancy. Our patients were diagnosed to have Factor VII deficiency after deranged coagulogram with Factor VII level of < 1% and 17.1%, respectively, however could be managed by fresh frozen plasma only in first case and fresh frozen plasma and Factor VII concentrate in second case successfully. Coagulation profile is a simple, easily available, affordable, and life-saving investigation to detect this deficiency in pregnancy. Decision regarding replacement therapy should be individualized on a case-to-case basis.

Keywords Factor VII · Coagulation · Hemorrhage · Pregnancy · Prothrombin time · Activated partial thromboplastin time

Introduction

Inherited Factor VII (FVII) deficiency is a rare coagulation disorder, the prevalence being 1:300,000 to 1:500,000 [1, 2] of severe form and 1 in 350 for heterozygotes [3].

FVII deficiency, autosomal recessive disorder, is associated with different bleeding manifestations varying from minimal to life-threatening hemorrhage. The usual clinical presentation is bleeding into joints and muscles, excessive bruising, epistaxis, and menorrhagia. There is a somewhat poor association between bleeding tendency and absolute FVII level; scanty symptoms may occur in those with very low FVII levels, whereas those with higher levels may present with significant bleeding [4] making it difficult to identify which patients will require prophylactic replacement therapy prior to hemostatic challenges or surgical intervention [5]. FVII deficiency in reproductive age women can manifest as menorrhagia, metrorrhagia, excessive bleeding after abortion, and antepartum or postpartum hemorrhage [3, 6]. Those with less than 1% FVII activity usually suffer from a severe bleeding disorder similar to hemophilia [7]. FVII deficiency should be suspected in all women with a history of bleeding and prolonged prothrombin time (PT) with normal activated partial thromboplastin time (APTT) [8]. Less than 100 pregnant women (Table 1) have been reported with FVII deficiency [5, 7–14] so far. We, hereby, report 2 cases of pregnancy with FVII deficiency along with a review of the literature.

✉ Rakhi Rai
drrakhi81@yahoo.co.in

Minakshi Rohilla
minurohilla@yahoo.com

Jasmina Ahluwalia
japgi@live.com

Pankaj Malhotra
malhotrapankaj@hotmail.com

Vanita Jain
drvanitajain@yahoo.com

1 Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, India

2 Department of Hematology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, India

3 Department of Medicine, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, India

Table 1 Review of literature of pregnant women with FVII deficiency

Author	Year	No. of women	FVII level	Clinical presentation at diagnosis	Mode of delivery	APH/PPH	Prophylaxis
Kreuziger et al. [5]	2013	62	Median–5.5%	Variable	53 vaginal, 31 cesarean	PPH in 10% with prophylaxis, 15% without prophylaxis	rFVIIa-FFP
Yazicioglu [9]	2013	1	35–46%	Abruptio placentae at 29wks gestation	Cesarean section	APH	
Das et al. [7]	2014	1	2 IU/dl	Menorrhagia, epistaxis	V.D	None	rFVII Oral tranexamic acid
Lee et al. [8]	2014	1	1.5–11%	Prolonged bleeding at dental extraction	C.S	None	FFP, tranexamic acid, vitamin K
Pinar et al. [10]	2015	1	1%	Known case of FVII deficiency	Dilatation and curettage at 9 weeks POG	None	
Pfrepper et al. [11]	2017	1	1%	Known case of FVII deficiency with history of menorrhagia & mucocutaneous bleed	VD	None	rFVIIa
Loddo et al. [12]	2019	1	18%	Known case of FVII deficiency with history of minor bleeding in past	VD	None	rFVIIa
Hasoon et al. [13]	2020	1	21%	Known case of FVII deficiency	VD	Traumatic PPH	None
Lee et al. [14]	2020	5 patients, 6 deliveries	<1 to 29%		3 VD, 3 CS	PPH (laceration in 1, uterine atony in another patient could be contributing factors)	rFVIIa in 2 patients, FFP in 1, none in 2 patients
Rohilla et al	2016	1	<1%	During routine investigations, previous history of PPH	VD	PPH in previous pregnancy	FFP
	2018	1	17.1%	Antepartum hemorrhage	Lower segment cesarean section	APH	FFPs/FVII

VD Vaginal delivery, *CS* Caesarean section, *APH* Antepartum haemorrhage, *PPH* Postpartum haemorrhage, *FFP* Fresh frozen plasma

Case Report 1

Thirty-two-year-old second gravida, referred in view of deranged coagulogram, at term gestation. She was diagnosed with chronic hypertension at 16 weeks period of gestation (POG) and her blood pressure was well controlled on a minimal dose of labetolol. Antenatal period was uncomplicated till 37 weeks POG when coagulogram showed prolonged PT of 100 s (control 13 s) and normal APTT of (control: 25–32 s) 26 to 28 s on several occasions. She revealed a history of gum bleeding while brushing teeth for the last 1 month; otherwise, there was no history of menorrhagia, epistaxis, petechiae, joint swelling, or other bleeding manifestations. There was no history of bleeding disorders or consanguineous marriage in the family. During the last delivery, she had a history of traumatic postpartum hemorrhage (PPH), which was managed conservatively with vaginal packing and blood products. The liver function tests (LFTs) were normal. Her Factor VII level found to be less than 1% and, hence, diagnosis of FVII deficiency was reached. Six units of fresh frozen plasma (FFP) (each unit of FFP contains 180–200 ml plasma) and two vials (2.4 mg) of recombinant FVIIa (each vial of 1.2 mg contains 1200 µg of sterile white lyophilized powder of rFVIIa) were kept ready to manage postpartum hemorrhage in view of low FVII levels and induction of labor was done with oxytocin at 37 weeks 3 days POG in view of increased blood pressure records. She delivered a vaginally live-born baby of 2.6 kg with an Apgar score of 8, 9. Prophylactically two units of FFP were transfused intrapartum. There was no intrapartum or postpartum hemorrhage. Both mother and baby were discharged on day 3 postpartum in a satisfactory condition. Factor VII level was confirmed after delivery and was found to be the same at 3 months post-delivery. Her siblings were also advised for screening for factor 7 deficiency.

Case Report 2

Twenty-seven-year-old primigravida came at 36 weeks POG with multiple episodes of vaginal bleeding from 32 weeks POG. During the investigation, her prothrombin time was found to be prolonged 20 s, prothrombin index 62% with normal APTT of 28 s. LFT was within normal limits and serum level of FVII was found to be 17.1%. There was no history of excessive bruising or bleeding from any other site of the body. She was transfused FFPs and 1 vial of rFVIIa (each vial of 1.2 mg contains 1200 µg of sterile white lyophilized powder of rFVIIa) preoperatively and taken up for cesarean section (C.S) in view of placenta previa. She delivered a live-born boy of 2.8 kg with an Apgar score of 8, 9. There was no history of any intrapartum or postpartum complications. No blood or FFP transfusions were required intraoperatively. Both mother and baby were discharged in a satisfactory condition.

Methodology

We searched electronic medical databases using keywords rFVII, pregnancy, prolonged prothrombin time, and factor deficiency. Bibliographies of included articles were reviewed and relevant articles were included.

Discussion

FVII has a pivotal role in coagulation in vivo. Vascular injury leads to binding of activated FVII to tissue factor (TF), initiating coagulation and generating a concentration of thrombin at the place of vascular damage [15].

FVII deficiency was first recognized in 1951 by Alexander [16]. Patients with heterozygous genotype are typically asymptomatic whereas homozygous or compound heterozygotes develop bleeding manifestations. FVII levels are generally less than 10% of the normal values in homozygous or double heterozygous carriers in inherited FVII deficiency however may be approximately 20 to 60% in heterozygous carriers [5]. FVII level was less than 1% in the first and 17.1% in the second case with no hemorrhagic manifestations following delivery. FVII deficiency may be seen in chronic liver disease, warfarin users, vitamin K deficiency secondary to long-term antibiotic use, bile duct obstruction, or poor intestinal absorption [8]. FVII deficiency was probably congenital, since no other etiology was apparent in present cases which were managed with FFPs and FVII concentrates.

In reported cases, PT and APTT were performed multiple times as was done in our cases also and each time PT was prolonged and APTT was normal and, hence, a deficiency of Factor VII was suspected.

Women with heterozygous FVII deficiency have significantly higher FVII levels [6] with an insignificant increase in FVII levels during pregnancy in women with homozygous (severe) FVII deficiency [17–20]. According to a comprehensive analysis of two international registries of patients with congenital FVII deficiency (STER, Seven Treatment Evaluation Registry, and IRF7, International Registry of FVII deficiency), gynecological bleed is strongly predicted by mucocutaneous bleeds and the most common type of bleeding prevalent is menorrhagia. Hence, family should be educated to remain prepared to tackle menorrhagia at menarche. FVII levels < 3% are predictive of gynecologic bleed. Long-term FVII prophylaxis and systematic FVII

replacement may decrease menorrhagia, iron loss, and hysterectomy rate [21]. The risk of bleeding might be more in early pregnancy as compared to at term because of insufficient rise in FVII levels in early pregnancy [6]. In our cases, FVII level was estimated at term or near-term gestation with very low levels. This suggests that probably these patients were homozygous or double heterozygous for a mutation in the FVII gene.

There are no clear guidelines regarding replacement therapy (RT). According to STER Registry, a higher number of RT doses for a long duration are required in patients with FVII levels < 3%. The only predictor of RT duration and dose is the history of major bleed [22]. Management of inherited FVII deficiency includes RT with FFPs, Factor VII concentrates, prothrombin complex concentrates, and/or recombinant FVIIa (rFVIIa) [1]. Decision regarding RT therapy should be individualized on a case-to-case basis [13]. Previous bleeding episodes, recent FVII levels, mode of delivery, and anticipated surgical intervention determine the decision about the treatment [5]. Despite a poor correlation of low FVII levels, the most serious bleeding has been linked with postpartum hemorrhage (PPH) and surgery [7, 23]. Perioperative RT of ~ 20ug/kg FVII is effective in 95.5% cases, repeated ~ 8 times in patients with major bleeding history. Single dose is an option in the absence of bleeding history [22]. The treatment of choice is recombinant Factor VIIa; however, there is a small risk of disseminated intravascular coagulation and thromboembolic complications with Factor VII concentrate [22, 24]. Disadvantages of FFP are volume overload and the possibility of blood-borne infections [24]. As our first case had a history of postpartum hemorrhage in previous pregnancy and had severe FVII deficiency in index pregnancy, 2 units of rFVIIa were arranged but could be managed with FFPs. Prolonged second stage of labor and instrumental delivery which increases the risk of neonatal hemorrhage should be avoided [3].

Only a few pregnant women (less than 100) have been reported so far with Factor VII deficiency [5, 7–14]. In a study by Baumann Kreuziger et al. [5], median FVII activity was 5.5%. Seventy-six percent of women had levels less than 10% and 82% had levels less than 20%. Similar FVII levels were found in women with or without a history of bleeding. Hemostatic prophylaxis was used in 30 deliveries with recombinant FVII in 17 deliveries, FFP and FVII concentrate in 6 deliveries each, and both FVII concentrate and FFP in one delivery [5]. Similar to the first index case, the case series included 8 women with FVII level < 1%. Five women were delivered vaginally and 3 by C.S. All 3 women who had cesarean sections received rFVIIa as prophylaxis, and in the vaginal delivery group, one woman received FFP. Out of these eight patients, one had postpartum hemorrhage during cesarean despite receiving rFVIIa [16]. The rate of hemorrhage was similar in the women who received prophylaxis and those who didn't. Hence, hemostatic prophylaxis is not necessary in all cases and should be individualized [5]. Yazicioglu et al. [9] reported a case of FVII deficiency presenting as abruptio placentae at 29 weeks POG and was managed without any replacement therapy. Similar to the first case, recently, a case report of pregnancy in a known patient with FVII deficiency was successfully managed with antifibrinolytics and FFPs [8]. Pinar et al. [10] reported dilatation and curettage at 9 weeks POG in a patient with FVII deficiency after prophylactic administration of FVII [10]. Pfrepper et al. [11] and Loddo et al. [12] reported one case each of FVII deficiency managed by rFVIIa. Lee et al. [14] reported a case series of 5 patients with 6 deliveries (3 vaginal deliveries and 3 cesarean sections). Two patients with severe deficiency received rFVIIa. Early PPH occurred in 2 patients but vaginal laceration and uterine atony could be contributing factors in them respectively. None of the patients had delayed PPH. Delayed postpartum hemorrhage may occur secondary to acute drop in FVII levels after pregnancy; hence, patients must be observed for 72 h postpartum [13].

Prenatal diagnosis should be offered to parents by chorionic villus sampling/amniocentesis/cordocentesis to those parents who had severely affected child or when both parents are heterozygous carriers. Physiologically low levels in newborns make it difficult to diagnose FVII deficiency in the neonatal period but FVII levels should be determined from cord blood at the time of delivery if severe deficiency is suspected [3]. Families must be educated about the risks of consanguinity in order to decrease the burden of certain inherited disorders. The most appropriate intervention would be gene therapy with its curative potential [25].

Conclusion

Considering the rarity of FVII deficiency, obstetrician needs to have a very high index of suspicion to identify these cases and prevent morbidity. Coagulation profile is a simple, easily available, and affordable investigation which can easily detect these cases and save lives. Replacement therapy and hemostatic prophylaxis are not necessary in all cases and should be individualized depending upon the Factor VII levels and previous bleeding manifestations. Appropriate counselling of the mother regarding the possibility of antenatal complications plays an integral part in the continuation of such pregnancies.

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Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Consent was taken from the patients.

Consent for Publication Consent was taken from the patients.

Conflict of Interest The authors declare no competing interests.

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Patient Perspective We were satisfied with the management. We were not aware of the FVII deficiency. The diagnosis will help us in planning future pregnancies. We will be more careful in our day-to-day activities to prevent any injury.