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Factor VII Deficiency and Sepsis in Pregnancy Treated with Recombinant Factor VIIa

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Abstract

Inherited factor VII deficiency is a rare autosomal recessive coagulation disorder, classified as type 1 or type 2 depending on the absence or presence of factor VII antigen in plasma. There are only few published case reports in the literature guiding management of factor VII deficiency specifically in obstetric patients. We would like to report anaesthetic management of a factor VII deficiency during pregnancy, which was complicated by sepsis.

Keywords: Factor VII deficiency; Pregnancy

Introduction

Factor VII is a vitamin K dependent clotting factor and a proenzyme. The active form of the enzyme is factor VIIa. Factor VIIa plays an important role at initiation, amplification and propagation of the haemostatic process proposed by the cell-based coagulation model [1]. Congenital Factor VII deficiency is a rare autosomal recessive disorder with variable expression, which can manifest as a wide spectrum of clinical phenotypes [2]. The disorder has an estimated incidence of one in 500,000; however, the severity of haemorrhage does not always correlate with the factor VII level [3,4]. Pregnancy is associated with a hypercoagulable state. Factor VII level is elevated in normal women during pregnancy whereas there is no significant increase in homozygous deficiency [5]. In general, maintaining a factor VII level of at least 15-25% of normal provides adequate haemostasis for most surgical procedures. Haemorrhage can become evident at levels less than 10IU/dL. Heterozygous carriers of factor VII mutations may manifest with mild disease with associated level of 20-60 IU/dL [6]. There are a few documented case reports of factor VII deficiency in pregnancy in the literature, each of which receives a different treatment regimen with no standardization [6-9]. We report a case of a parturient woman with mild factor VII deficiency, further complicated by pregnancy induced thrombocytopenia and urinary sepsis.

Case Report

A 27 year old Gravida 3, Para 2 women was diagnosed with mild Factor VII deficiency after two previous significant postpartum haemorrhages. In both cases, transfusion of packed red cells and platelets was required but not recombinant factor VIIa. Her factor VII level was normally 24–35 IU/dL (Lab normal range: 50-150 IU/dL). She was seen antenatally by the obstetrician at 10 weeks and commenced on vitamin K 10mg once a day. She presented to the Accident and Emergency department at 28 weeks gestation with haematuria. She was apyrexic, and had no cardiovascular compromise. There were no signs and symptoms indicating infectious causes. Her blood results at this point revealed haemoglobin10g/dL, factor VII 54.4 IU/dL, platelet count $83x10^9$/l with a normal clotting profile. Ultrasound and MRI showed bilateral gestational hydronephrosis. The haematuria resolved spontaneously after one day. CTG monitoring showed no concerns with the foetus. At 38+5 weeks gestation, she was admitted to antenatal ward with right renal angle pain without haematuria. A urinary tract infection was diagnosed by positive urine dipstick of white cell, nitrate, protein and blood. Her WCC was 8.9 x 10^9, CRP was 31. Her vital signs were normal. Gentamicin was started as patient was allergic to penicillin. Over a 24 hour period she became more septic with pyrexia, tachypnea, tachycardia, hypotensive and compensated metabolic acidosis, which required admission to HDU for closer monitoring and fluid resuscitation. Continuous CTG monitoring did not show any sign of foetal compromise. Urine sample showed heavy growth of Group B streptococcus, which was sensitive to Ciprofloxacin and resistant to Gentamicin. She responded well to the change of antibiotics, with improved perfusion and acidosis. Her INR, APTT ratio, platelet count and Factor VII levels were monitored (Table 1). There was no clinical evidence of haemorrhage, however, in view of her dramatic drop of factor VII level and thrombocytopenia, she was given two pools of platelets, and a single dose of recombinant factor VIIa 1mg (15µg/kg) on day 2 of hospital admission. Spontaneous rupture of membrane occurred at day 3; continuous CTG monitoring since admission did not show any foetal concerns. Labour onset started at the end of day 4 since admission. Entonox was administered for labour analgesia, however, labour failed to progress. On the morning of day 5, a caesarean section under general anaesthesia was

Table 1. Serial Coagulation Profile

Admission	Platelet count (x10^9/l)	VII(IU/dL)	Hb(g/dL)	INR	APTT Ratio
Day 1	86	51.1	10.6	1.1	0.8
Day 2	52	11.8	10.8	1.7	1.2
15 µg/kg iv dose of recombinant factor VIIa					
Day 3	47	14.9	10.0	1.6	1.3
Day 4	67	36.7	10.2	1.3	1.3
Day 5	76	42.2	9.8	1.2	1.2
Caesarean under GA					
Day 6	86	40.1	9.9	1.2	1.2
Day 7	105	37.5	9.8	1.2	1.2

carried out. One pool of platelets was given prior to surgery. In theatre, after instituting all routine monitors, rapid sequence induction with intravenous thiopental 280mg followed by suxmethonium 100mg, intubated with a 7.0mm oral tube. The lungs were ventilated with a tidal volume of 500mls and frequency 12bpm after muscle relaxation with atracurium 30mg. Anaesthesia was maintained with 1 MAC of Sevoflurane. Induction to baby delivery time was 6.5 mins and a healthy male baby was delivered, with Apgar score 9 and weight 3560g. Surgery and anaesthesia were uneventful with approximate blood loss of 400mls which was replaced with crystalloid. The post-operative recovery period was uneventful. She was discharged on day 8. Both she and baby were doing well. Six weeks after discharge, her platelet count returned to normal 186 x 10^9/l, Factor VII level 32.4 IU/dL.

Discussion

The normal physiological rise of factor VII during pregnancy is impaired in cases with homozygous deficiency, but a case series revealed that women with mild to moderate disease show an increase in factor VII level from a mean baseline of 33IU/dL to 73IU/dL at term [5]. However, in this case, her sepsis might have contributed to the significant factor VII level drop. The management of Factor VII deficiency during pregnancy involves achieving a balance between haemostasis and preventing hypercoagulable state that will lead to thrombus formation. rFVIIa is a potent thrombin generator; thrombosis is an adverse effect of primary concern. In cases of high levels of tissue factor expression, thrombogenic potential of rFVIIa is increased [10]. In this case, she received a small dose of rFVIIa (15µg/kg), which led to a transient but significant factor VII level rise from 11.8 IU/dL to 637.6 IU/dL. She was closely monitored for any potential deep vein thrombosis development. Her arterial lines clotted three times; otherwise there were no signs of thrombus formation. Continuous infusion of low-dose rFVIIa might be an option to prevent such high level rise in plasma concentration.

There is some data supporting a dosing regime in non-obstetric patients [11]. But there are no clear guidelines for the use of rFVIIa in obstetric cases with factor VII deficiency. Due to its short half-life (approx. 2.7h), appropriate dosage was a problem in the few reported cases. The dose range was 50µg/kg to 10µg/kg with various intervals among the reported cases. Continuous infusion of rFVIIa has been recommended instead of a single dose in one case report [9]. In our case, at the time of receiving rFVIIa, she was not in labour and there were not any signs of haemorrhage. One could also argue that another option is not to administer rFVIIa, but treat her sepsis and continue to monitor factor VII plasma concentration, as it is expensive and also associated with adverse effect. A case report by Kolucki et al. [8] illustrated that clinical manifestations of inherited factor VII deficiency can widely vary, and the severity of clinical haemorrhage does not predictably correlate with the plasma level of factor VII. In view of her previous two episodes of significant postpartum haemorrhage, and complicated with pregnancy induced thrombocytopenia, choosing replacement therapy in this case is beneficial. Clinical decisions must be based on individual case scenario to weigh up risks and benefits as it is a rare condition.

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