Prophylactic treatment of hereditary severe factor VII deficiency in pregnancy

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Severe hereditary factor VII deficiency is a rare bleeding disorder and may be associated with a severe bleeding phenotype. We describe a pregnancy in a 33-year-old woman with compound heterozygous factor VII deficiency and a history of severe menorrhagia and mucocutaneous bleedings. After discontinuation of contraceptives, menstruation was covered with recombinant activated factor VII (rFVIIa), and during pregnancy, rFVIIa had to be administered in first trimester in doses ranging from 15 to 90 μg/kg per day because of recurrent retroplacental hematomas and vaginal bleedings. Thrombin generation was measured in first trimester at different doses of rFVIIa and showed an increase in lag time when doses of less than 30 μg/kg/day were administered, whereas time to thrombin peak and peak thrombin were not influenced. A low-dose rFVIIa prophylactic treatment of 15 μg/kg every other day in the late second and in the third trimester was sufficient to allow a successful childbirth in this patient with severe factor VII deficiency. *Blood Coagul Fibrinolysis* 27:000–000

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Introduction

Severe hereditary factor VII deficiency is a rare congenital bleeding disorder affecting about 1 : 500 000 people. Although most of the heterozygous patients with a factor VII activity between 20 and 60% have no bleeding tendency, homozygous or compound heterozygous patients have a factor VII activity of less than 10% depending on the genetic mutation. Although factor VII level does not correlate with bleeding tendency [1], patients with a factor VII level of less than 1% tend to be associated with a severe bleeding phenotype. Prophylactic administration of a factor VII concentrate may be indicated in some of these patients in early childhood [2]. According to a recent literature review [3], only very few deliveries in patients with severe factor VII deficiency of less than 1% have been described. In the entire described population with a median factor VII activity of 5.5%, prophylaxis was used in 32% of all deliveries, with a 10% incidence of postpartum hemorrhage compared with 13% in women not receiving prophylaxis. However, literature about prophylaxis in factor VII-deficient patients during pregnancy is very rare.

Case report

We report on a woman with a compound heterozygous factor VII deficiency with a factor VII activity of 1%. A combination of a double mutation Ala294Val;404delC that she inherited from her mother and a 55C>G mutation in the promoter region from her father was identified. First bleeding episodes occurred when her deciduous teeth broke through. She was diagnosed at the age of 6 years. At the age of 12 years, she was admitted twice for menorrhagia, which was treated with a prothrombin complex concentrate, methylergobrevin, and a sequential oral contraceptive containing ethinyl estradiol and norethisterone. The menorrhagia persisted, resulting in a management with prothrombin complex concentrates and recombinant activated factor VII (rFVIIa) when it became available. Nevertheless, repeated hospital admissions were necessary. Teeth extractions were managed after substitution of rFVIIa. Apart from menorrhagia, she had no spontaneous bleedings or joint bleeds.

At the age of 33 years, the patient, who was contemplating child bearing for almost 10 years, finally decided to become pregnant and hormonal contraceptive was discontinued. Menstruation was covered with rFVIIa at a dose of 30 μg/kg every 8 h for the first 48 h followed by 15 μg/kg every 8 h for another 24 h and 15 μg/kg every 12 h for the last 1–2 days. With this substitution, she had a normal blood loss during menstruation. This dose was known from episodes of menorrhagia earlier in her life. Six months after stopping contraception, a pregnancy at the fifth week of gestation was diagnosed. Bleeding

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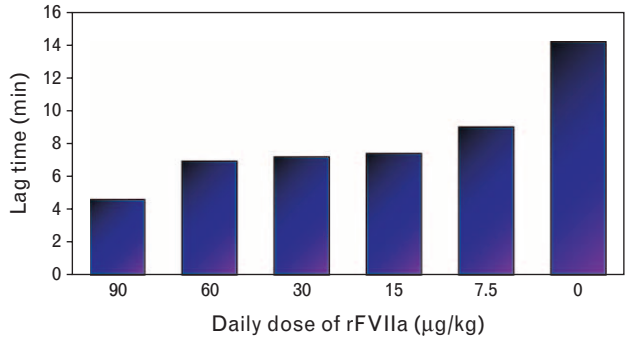
Fig. 1



Lag time of thrombin generation measured prior to substitution according to daily dose of recombinant activated factor VII administered (90 μg/kg in sixth gestational week, 60 μg/kg in eighth gestational week, 30 μg/kg in ninth gestational week, 15 μg/kg in 10th gestational week, 7.5 = 15 μg/kg every other day in 29th gestational week, without substitution measured 1.5 years after child birth on oral contraceptives).

prophylaxis was started at a dose of 30 μg/kg rFVIIa every 8 h. Despite this regimen, she developed a retroplacental hematoma 7 days later and rFVIIa dose was increased to 30 μg/kg every 6 h for 2 days and the hematoma subsided. The rFVIIa dose was then reduced to 30 μg/kg every 8 h and 4 days later to 30 μg/kg every 12 h.

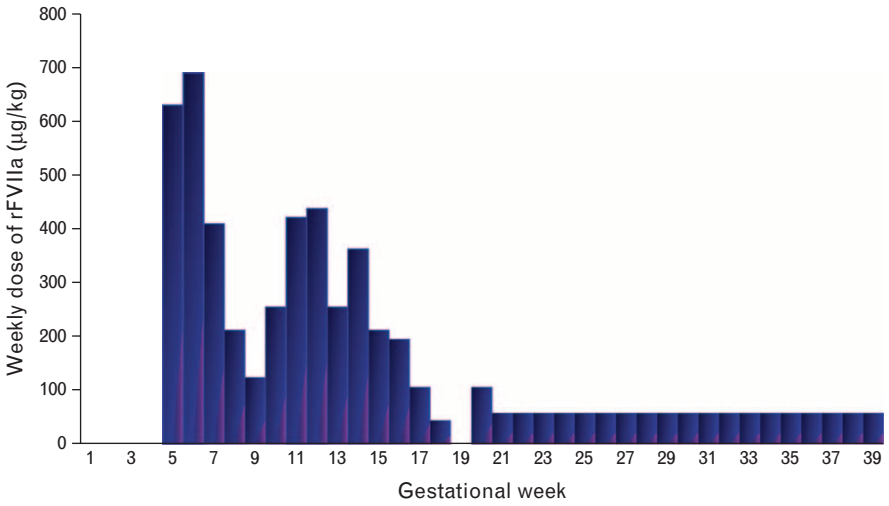
Gynecological ultrasonography was performed weekly to check for retroplacental hematoma. Based on the favorable ultrasound findings, the rFVIIa dose was decreased to 15 μg/kg every 12 h for a week and finally to 15 μg/kg daily. During this time in first trimester, thrombin generation was measured in platelet-poor plasma using the Technothrombin TGA kit (Technoclone, Vienna, Austria; method described in supplement, http://links.lww.com/BCF/A30). Thrombin generation measured before substitution showed a linear decrease in the thrombin generation lag time (TG-LT) with the daily dose of rFVIIa administered (Fig. 1), whereas time to thrombin peak, peak thrombin, and velocity index did not show any difference. Ten days after dose reduction of rFVIIa to 15 μg/kg daily, the woman reported vaginal bleeding, so that the dose had to be increased.

During the following weeks, recurrent retroplacental hematoma and slight vaginal bleedings were reported, so that rFVIIa dose was adjusted between 15 and 30 μg/kg once or twice daily. At the 18th gestational week, the bleeding tendency subsided and the rVIIa dose was reduced to 15 μg/kg every other day and discontinued 1 week later. Unfortunately, retroplacental hematoma was detected 1 week later. Therefore, rFVIIa prophylaxis of 15 μg/kg every other day until childbirth was administered. Substitution with rFVIIa during pregnancy is summarized in Fig. 2. Ultrasonography did not show any hematoma and the patient remained clinically stable. A vaginal delivery with 30 μg/kg rFVIIa every 8 h was successful at the 39th gestational week, with no increased bleeding tendency. The newborn child did not show any bleeding tendency and had a factor VII level of 54%.

Summary

This is to our knowledge the first case report on a successful delivery in a woman with compound heterozygous factor VII deficiency and a severe history of menorrhagia necessitating prophylactic coagulation factor substitution for menstruation and throughout

Fig. 2



Weekly dose of recombinant activated factor VII according to gestational week.

pregnancy. Thrombin generation assays showed a prolonged lag time while on rFVIIa dose less than 15 μg/kg per day. which was associated with a reappearance of bleeding in the first trimester. A low-dose rFVIIa prophylactic treatment of 15 μg/kg every other day in the late second and in the third trimester was sufficient to allow a successful childbirth.

Discussion

Literature about prophylaxis in factor VII deficiency is very rare. The reported cases of women with severe factor VII deficiency needed much less factor supply. In a report from the Seven Treatment Evaluation Registry [4] about the use of prophylaxis in 34 patients with congenital factor VII deficiency, only four patients were included receiving prophylaxis for menorrhagia, two of whom had a factor VII level of less than 1%. Dose of rFVIIa administered in these two women was 304 and 1204 μg/kg weekly in a long-term treatment. This was the same dose we administered to our patient during menstruation and first trimester. Lag time measured with thrombin generation seems to correlate with the substituted dose of rFVIIa and bleeding tendency in our patient. This finding is corresponding to other publications in which a delayed TG-LT but a normal thrombin peak and peak thrombin was found [5], whereas substitution of rFVIIa can correct the delayed lag time [6]. More data are needed to evaluate the capability of TG-LT to guide substitution.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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