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Pregnant Women with Severe Factor VII Deficiency Undergoing Cesarean Section Managed with a Short-Term Regimen of Recombinant Factor VIIa

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To editor:

Factor VII (FVII) is a determining factor in activating the exogenous coagulation pathway; F7 gene mutation decreases the FVII number or function. Factor VII deficiency (FVIID) is characterized by an isolated prolongation of the prothrombin time (PT) with a normal activated partial thromboplastin time (aPTT). Factor assay and genotyping for FVII can be done to confirm the diagnosis.[1,2] Patients may present with menorrhagia, and bleeding tendencies may vary from slight gingival bleeding, epistaxis, and ecchymosis, to severe bleeding, such as gastrointestinal and intracranial bleeding.[3] FVIID is classified according to the patients' FVII activity as mild: FVII 20%–50%, moderate: FVII 10%–20%, and severe: FVII <10%. Mild cases may be asymptomatic, while moderate and severe cases have a higher risk of spontaneous bleeding. However, the FVII level does not always correlate with the risk of bleeding, and this may make effective patient management complex as it requires a comprehensive understanding of the patient's bleeding pattern and treatment with appropriate clotting factor replacement therapy. We discussed managing two cases of asymptomatic parturients diagnosed with severe FVIID at our hospital. Both patients provided written informed consent for the publication of this report.

A 28-year-old primigravida with an abnormal clotting profile was referred to our hospital at 39 weeks and 1 day of gestation. Before pregnancy, her menstrual cycle was regular, with moderate bleeding for 4 to 5 days. She had no history of chronic illnesses and no history of menorrhagia or other abnormal bleeding tendencies. She had an uneventful appendectomy during her early teenage years and denied any familial bleeding disorders. She was diagnosed with FVIID after consecutive abnormal results on coagulation profile tests (PT: 30.3 seconds, aPTT: 52.1 seconds), with FVII activity of 3.0%. She had no discomfort or bleeding tendency at the time of diagnosis, so no treatment was given. She underwent successful in vitro fertilization and embryo transfer 6 months later after failing to conceive naturally because of obstructed fallopian tubes and endometrial adhesions. Her pregnancy progressed uneventfully, with prothrombin time fluctuating between 24 and 43 seconds. She reported no bleeding from her gums, nose, or gastrointestinal tract and had no intracranial bleeding during the pregnancy.

On admission, her blood pressure was 145/88 mm Hg, and the rest of the physical examination was unremarkable. Laboratory tests revealed urine protein +2, PT: 34.9 seconds, aPTT: 30.9 seconds, international normalized ratio (INR): 3.19%, with FVII activity at 4.7%. At 39 weeks and 2 days of gestation, after multidisciplinary team discussions, she underwent a cesarean section under general anesthesia because of late-onset preeclampsia. Two milligrams of rFVIIa (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) were administered 3 hours preoperatively, and a uterine tamponade was placed intraoperatively after she developed uterine atony. Intraoperative bleeding was 400 mL, and the total 24-hour postpartum bleeding was 850 mL. A further 2 mg of rFVIIa (25 μg/kg) was administered 4 hours postoperatively and once on the first and second postoperative days. Coagulation function test results during her hospital stay are shown in Figure 1. A healthy 3450 g female baby was delivered, and the baby's coagulation function test revealed PT: 11.7 seconds, INR: 1.09%, and aPTT 49.6 seconds. Both mother and baby were discharged 6 days postoperatively in good condition.

A second case involved a 32-year-old gravida 3 para 1, admitted to our hospital due to abnormal coagulation function. Eleven years before the current hospital admission, she underwent two uneventful exploratory laparotomies, one due to ruptured corpus luteum and another due to acute perforated appendicitis. Six years before the current admission, she was diagnosed with FVIID during her first pregnancy and was later managed with 800 U of prothrombin complex before and during delivery of a 2300 g female baby born after premature rupture of fetal membranes. She sustained a first-degree perineum laceration with minimal bleeding and recovered fully. Four years before the current admission, she had a spontaneous abortion at 50 days of pregnancy without excessive bleeding. She had no history of chronic illnesses, menorrhagia, or other abnormal bleeding tendencies. Abnormal coagulation function was detected at 9 weeks of gestation during the current pregnancy, but no follow-up testing was done because she did not regularly attend antenatal care. She was referred to our hospital at

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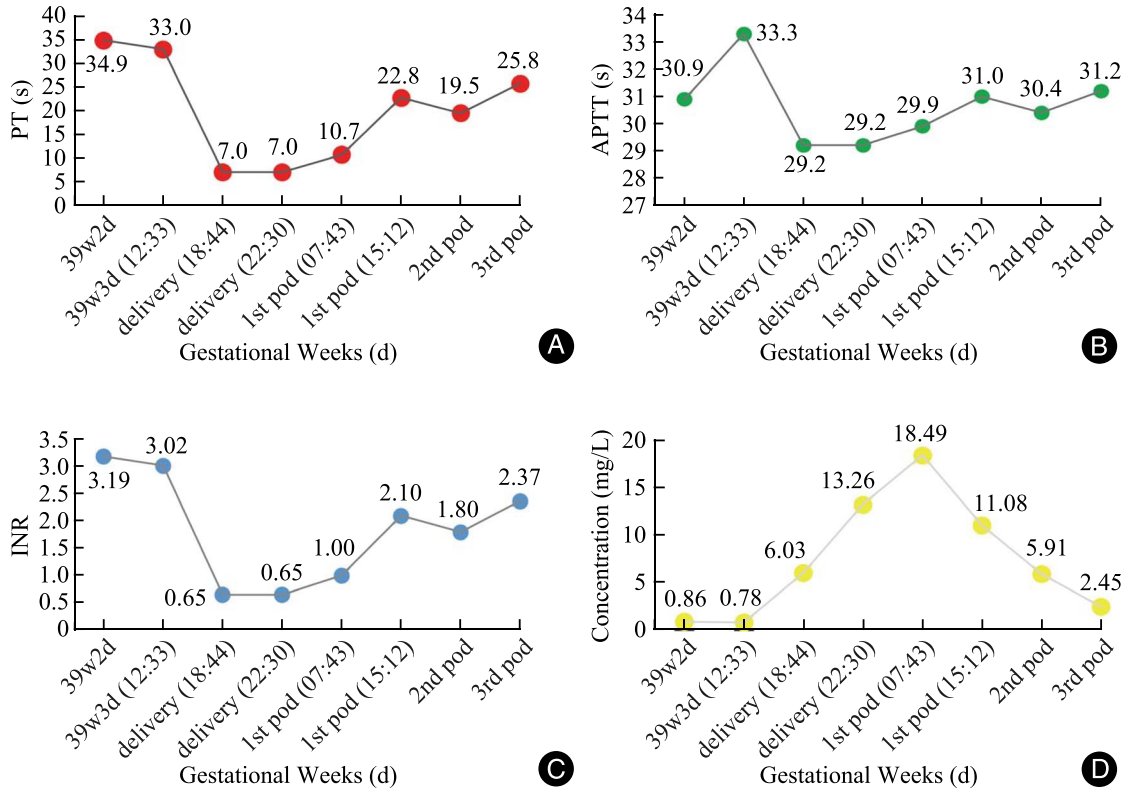

Figure 1. Blood clotting parameters of case 1 during the hospital stay. A Prothrombin time. B Activated partial thromboplastin time. C International normalized ratio. D D-dimer; pod: Postoperative day.

38 weeks and 4 days of gestation after a review of her coagulation function (PT: 53.3 seconds, INR: 4.78%, fibrinogen: 5.36 g/L, and thrombin time: 15.9 seconds).

On admission, her physical examination was unremarkable, and coagulation tests showed PT: 134.0 seconds, INR: 11.91%, FVII activity of 2.2%, and an obstetric ultrasound reported oligohydramnios. Fetal distress was suspected at 40 weeks and 0 days of gestation, and after multidisciplinary consultation, an emergency cesarean section under general anesthesia was done on the same day. Two milligrams of rFVIIa (25 μg/kg) was administered before the operation, and a 3200 g male baby was delivered. The intraoperative bleeding was 300 mL, and 24-hour postpartum bleeding was 400 mL. Two milligrams of rFVIIa was administered 10 hours postoperatively and a further dose on the first postoperative day. The patients' postoperative coagulation function parameters are shown in Figure 2. The neonate had an FVII activity of 23.5% after delivery and was sent for observation in the neonatal department. The mother and baby were discharged in good condition on the sixth postoperative day.

Discussion

FVII is an autosomal recessive bleeding disorder mainly caused by F7 gene point mutations on chromosome 13, and missense mutations are the most frequent variants.[2] Typically, a homozygote or compound heterozygote individual has a significant genetic mutation with severe deficiency (prevalence 1:500,000), while heterozygous individuals have higher FVII activity 20% to 60% (prevalence 1:350).[4] Congenital FVIID can present as life-threatening intracranial or gastrointestinal tract bleeding in the first half-year of life.[5] In our case report, the baby born in the second case had reduced FVII activity (23.5%), but no bleeding or easy bruising was reported during hospitalization and at 5 months after discharge, but the mother was not keen on following up her coagulation function tests. This presents a challenge because FVII activity can fluctuate in response to various factors, such as stress, infections, medications, or hormonal changes, affecting the severity and frequency of bleeding episodes.[6] Therefore, regularly monitoring FVII levels and bleeding symptoms is essential to adjust the treatment plan.

There are currently no specific guidelines for managing parturients with FVIID. Available literature does not clarify if prophylactic agents during labor or delivery can improve maternal or fetal outcomes.[7] Based on previous case reports and analyses, it has been suggested that patients with severe FVIID (FVII <10%) may require prophylactic treatment. Furthermore, the patients' FVII activity, clinical manifestations, and bleeding history should be carefully considered before deciding on rFVIIa prophylaxis, a preferred agent.[4,8] In our case report, our patients both had severe FVIID (FVII < 5%) throughout their pregnancy but did not report any history of bleeding abnormal bleeding. We administered prophylaxis with a 25-μg/kg dose of rFVIIa before cesarean section and

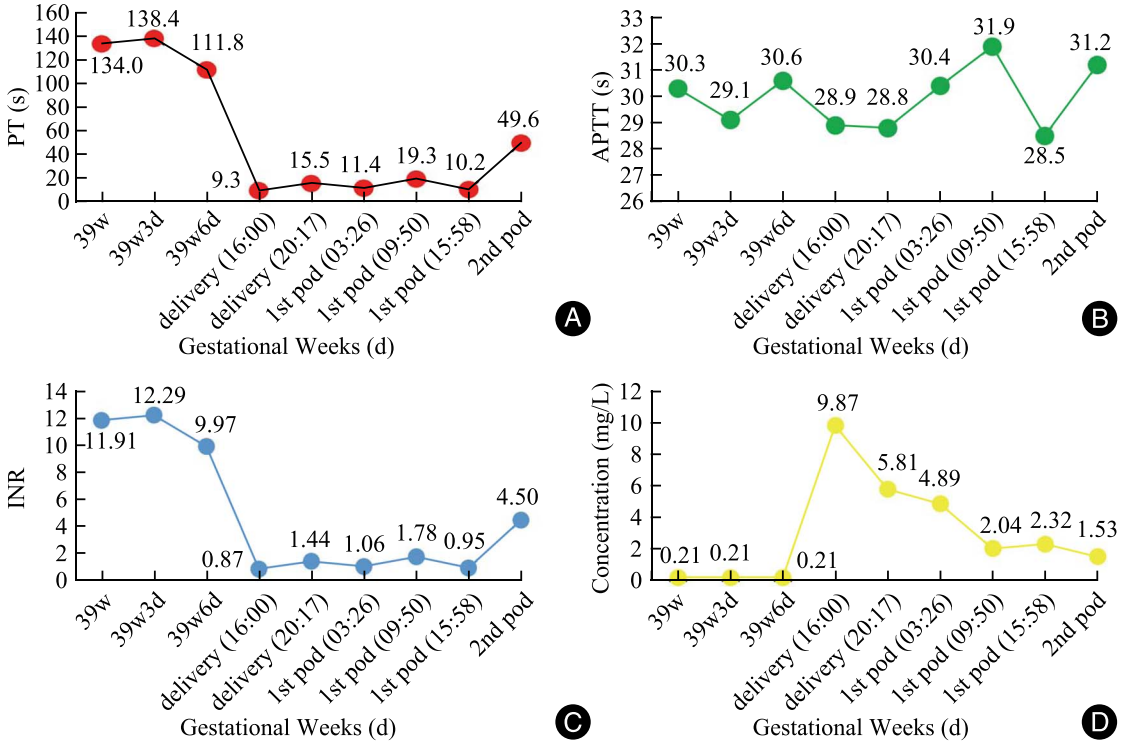

Figure 2. Blood clotting parameters of case 2. A Prothrombin time. B Activated partial thromboplastin time. C International normalized ratio. D D-dimer; pod: Postoperative day.

gave two more single doses postoperatively. The short course regimen of rFVIIa that we opted for proved effective in preventing severe hemorrhage. The rFVIIa was administered shortly before the operation to provide optimum coverage as the half-life of rFVIIa is approximately 3 hours,[6] and the regimen was influential in the correction of the clotting parameters, as seen in Figures 1 and 2 above. Both patients had their coagulation function closely monitored after admission, during the perioperative period, and before discharge. Multidisciplinary team discussions that included hematology, anesthesiology, pharmacy, critical care medicine, and neonatology department specialists created an appropriate treatment plan for our patients. This was critical in minimizing the risk of adverse outcomes and provided valuable input in the holistic management of patients, as has previously been recommended for patients with bleeding disorders.[9] Cesarean section under general anesthesia was preferred for the patient to avoid any associated adverse outcomes like neuraxial hematoma that might be associated with neuraxial or spinal anesthesia.[10]

The pregnancy outcome of the patients we report here was satisfactory, with no postpartum hemorrhage. On follow-up, both patients reported good puerperal recovery, both had FVII activity <15% at 42 days after delivery, and their babies did not have any abnormal bleeding tendency. It is essential to test patients' FVII activity after administration of rFVII preoperatively and postoperatively to evaluate the therapeutic effect of rFVIIa better.

Conclusion

Safe perinatal management of pregnant women with FVIID during cesarean section delivery should involve close observation. Serial sampling of perioperatively coagulation function indices may be necessary for monitoring the patient's condition, and the neonate should also be followed up.

Funding

None.

Conflicts of Interest

None.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

References

[1] Lee EJ, Burey L, Abramovitz S, et al. Management of pregnancy in women with factor VII deficiency: a case series. Haemophilia 2020; 26(4):652–656. doi: 10.1111/hae.14086.

[2] Bernardi F, Mariani G. Biochemical, molecular and clinical aspects of coagulation factor VII and its role in hemostasis and thrombosis. Haematologica 2021;106(2):351–362. doi: 10.3324/haematol.2020.248542.

[3] Winikoff R, Scully MF, Robinson KS. Women and inherited bleeding disorders—a review with a focus on key challenges for 2019. Transfus Apher Sci 2019;58(5):613–622. doi: 10.1016/j.transci.2019.08.013.
[4] Loddo A, Cornacchia S, Cane FL, et al. Prophylaxis of peripartum haemorrhage using recombinant factor VIIa (rfVIIa) in pregnant women with congenital factor VII deficiency: a case report and literature review. Eur J Obstet Gynecol Reprod Biol 2019;235:77–80. doi: 10.1016/j.ejogrb.2019.02.017.
[5] Shahbazi S, Mahdian R. Factor VII gene defects: review of functional studies and their clinical implications. Iran Biomed J 2019;23(3):165–174. doi: 10.29252/.23.3.165.
[6] Sevenet PO, Kaczor DA, Depasse F. Factor VII deficiency: from basics to clinical laboratory diagnosis and patient management. Clin Appl Thromb Hemost 2017;23(7):703–710. doi: 10.1177/1076029616670257.
[7] Shapiro A. The use of prophylaxis in the treatment of rare bleeding disorders. Thromb Res 2020;196:590–602. doi: 10.1016/j.thromres.2019.07.014.
[8] Hajjar R, Hatoum I, Krounbi A, et al. Pregnancy in a woman with congenital F-VII deficiency: a brief review of recent literature and case report. Hematol Transfus Cell Ther 2021;S2531-1379(21)00125-5. doi: 10.1016/j.htct.2021.07.003.
[9] Yang Y, Zeng YC, Rumende P, et al. Diagnosis and treatment discussion of congenital factor VII deficiency in pregnancy: a case report. World J Clin Cases 2021;9(21):6091–6101. doi: 10.12998/wjcc.v9.i21.6091.
[10] Demers C, Derzko C, David M, et al. No. 163-gynaecological and obstetric management of women with inherited bleeding disorders. J Obstet Gynaecol Can 2018;40(2):e91–e103. doi: 10.1016/j.jogc.2017.11.036.

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