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# Treatment with Recombinant Factor XIII (Tretten) in a Pregnant Woman with Factor XIII Deficiency

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Conflict of interest:** None declared

**Patient:** Female, 37
**Final Diagnosis:** Factor XIII deficiency
**Symptoms:** Bleeding • miscarriage
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Hematology

**Objective:** Rare disease
**Background:** Factor XIII deficiency is associated with recurrent miscarriages in women.
**Case Report:** In this report, we present a patient with factor XIII deficiency and some comorbidities who had had previous miscarriages. She began treatment with factor XIII subunit A (XIII-A) replacement treatment Recombinant factor XIII (Tretten) at a dose of 2500 units monthly and was able, for the first time, to carry a pregnancy almost to term. Although she experienced some obstetrical complications, she delivered a healthy baby. To the best of our knowledge, this is the first report of the use of Tretten during pregnancy.
**Conclusions:** Tretten, which is not indicated in pregnancy, offered a safe, effective treatment for miscarriages secondary to factor XIII-A deficiency in our patient. Further research is required to confirm this finding.

**MeSH Keywords:** Abortion, Spontaneous • Factor XIII Deficiency • Pregnancy Complications, Hematologic

**Full-text PDF:** http://www.amjcaserep.com/abstract/index/idArt/901502

## Background

Factor XIII is an important plasma protein in the clotting cascade. Initially termed fibrin stabilizing factor [1], factor XIII has since been found to play other important roles in hemostasis. It can crosslink various proteins not only in plasma but also in platelets, endothelial cells, monocytes, and proteins in the vascular matrix. Factor XIII is a heterotetramer that circulates in the plasma and is composed of 2 A and 2 B subunits. Factor XIII is converted by thrombin into activated factor XIII, in the presence of calcium. Factor XIII-a crosslinks between fibrin molecules and consequently helps to form and stabilize the thrombus [2].

Factor XIII deficiency can cause a tendency toward severe bleeding. It is very rare, with a reported incidence of 1 in 5 million people [3]. Most people with this disorder have a mutation in the subunit A gene located on chromosome 6p25-24, which is inherited in an autosomal recessive manner. However, 153 mutations in FXIII-A gene and 16 mutations in FXIII-B gene have been identified to date [4]; therefore, this disorder is characterized by a high degree of heterogeneity. As a result, factor XIII deficiency presents with a variety of clinical manifestations, and the clinical symptoms can range in severity. The disorder can present with hemorrhage during the neonatal period, or it may be diagnosed after delayed soft-tissue bruising, mucosal bleeding, or life-threatening intracranial hemorrhage. Patients with this disorder face a lifelong threat of hemorrhage; however, currently available prophylactic treatments offer a very good prognosis [5].

The clinical presentation of factor XIII deficiency includes severe bleeding, intracranial hemorrhages, poor wound healing, spontaneous abortions, and repeated post-tonsillectomy bleeding in undiagnosed hematological condition patients [6]. Most patients experience bleeding episodes throughout their lives, from birth onwards. At birth, bleeding from the umbilical cord manifests as persistent oozing lasting several days. In older individuals, there can be bleeding in the central nervous system, sometimes associated with trauma; the signs will depend on the location of the bleeding. It is uncommon for patients with factor XIII deficiency to present with large hematomas or joint bleeds, unlike patients with severe hemophilia. Female patients commonly experience vaginal spotting or bleeding during the first trimester of pregnancy, which often leads to a spontaneous miscarriage [5]. Morbidity and mortality was studied in a large series of patients (317) in Iran, a country that has about one-third of the world's patients with severe factor XIII deficiency [7]. It was noted that 15.4% of the patients in this study died as a result of umbilical cord bleeding or other symptoms, which underlines the importance of early diagnosis and appropriate care.

The diagnosis of factor XIII deficiency requires various tests. A routine evaluation of any bleeding disorder that includes tests for partial thromboplastin time, prothrombin time, thrombin, fibrinogen level, platelet count, and bleeding time would not lead to a diagnosis for factor XIII deficiency, because results for these tests can be within normal parameters in patients with this disorder. Clot solubility testing has been used since the 1960s to diagnose factor XIII deficiency, but this test can only detect severe cases. The mild to moderate forms of factor XIII deficiency are diagnosed through factor XIII activity assays. These quantitative assays include amine incorporation and ammonia release assays. Given that a variety of mutations cause factor XIII deficiency, genetic testing is also needed to pinpoint the type of mutation that individual patients carry [5]. Dorgalaleh et al. proposed a flexible, reliable algorithm for the diagnosis of factor XIII deficiency that could be applied in different parts of the world, taking into consideration variations in the sophistication of laboratory facilities and the ethnic origins of patients in different countries [8].

Factor XIII deficiency poses various challenges during pregnancy and delivery, and the management of pregnant women with this disorder requires a multidisciplinary approach. There is an increased risk of antepartum bleeding, and postpartum hemorrhage, defined as bleeding that exceeds 500 mL after vaginal delivery or 1000 mL after Cesarean delivery, is an important risk in the perinatal period [9]. As a general guideline, the plasma level of factor XIII subunit A must be at least 2–3 IU/dL, or ideally higher than 10–12 IU/dL, in pregnant women with factor XIII deficiency, and pregnant patients may need to be treated with factor XIII-A concentrate approximately every 7 days. The recommended dose is 10 IU/kg, to achieve a successful delivery [4]. During labor the plasma level of factor XIII subunit A should ideally be above 20 IU/dL; a more recent study suggested that it should be above 35 IU/dL [4]. To achieve this optimal level, a booster dose of 1000 IU of factor XIII-A concentrate should be administered [4,10]. To prevent postpartum hemorrhage, a dose of 250 IU weekly until the 23$^{rd}$ week was recommended, which should then be increased to 500 IU weekly [4].

The therapeutic options currently available include fresh frozen plasma at a dose of 10 ml/kg, cryoprecipitate at a dose of 1 bag/10 kg, and Fibrogammin and Corifact (factor XIII concentrate) at a dose of 10–26 IU/kg. Recombinant factor XIII-A was approved by the US Food and Drug Administration (FDA) in December 2013, at a dose of 35 IU/kg.

## Case Report

A 37-year-old female patient with factor XIII deficiency wished to become pregnant. She has 1 brother, but she does not have family history of this bleeding disorder. Her disease was

diagnosed at puberty, after she presented with bruises and heavy menstrual cycles. After thorough investigations, which revealed normal blood count, coagulation test results and platelet aggregation, the clot solubility test for factor XIII showed no clot present. Factor XIII activity was not assessed at that time. She had been treated with fresh frozen plasma once per month until the age of 18, when she started treatment once per month with Fibrogammin, a purified concentrate of factor XIII that is derived from human plasma. The patient was morbidly obese and had tested positive for hepatitis C but this infection had not been active and had not required treatment. The patient had not experienced major bleeding but she often had bruising and heavy menstrual cycles. She had been assessed on a yearly basis in our clinic, and the solubility test showed clot present most of the time. This reflected that fact that she received monthly factor replacement. In 2012, she suffered a miscarriage at 11 weeks' gestation that was related to her factor XIII deficiency. She underwent dilation, curettage, and suction without any complications, after receiving factor XIII (Fibrogammin) the day before. The patient wished to become pregnant again, thus she was tested at the reference laboratory and found to have factor XIII activity of 5 IU/dL (reference of 60 to 169 IU/dL) and factor XIII-A activity of 4 IU/dL (49 to 154 IU/dL). She began treatment with Tretten, a recombinant analogue of the A subunit of factor XIII, at a dose of 2500 units monthly. After the patient became pregnant, she developed gestational diabetes and at 36 weeks' gestation she developed HELLP syndrome, which is characterized by hemolysis (absolute reticulocyte count was $130\times10^9$/L, LDH 420 U/L), elevated liver enzymes (gamma glutamyl transpeptidase was 72 U/L, aspartate amino transferase 238 U/L, alanine amino transferase 330 U/L, alkaline phosphatase 243 U/L), and a low platelet count ($76\times10^9$/L in this case). At this time she was admitted to hospital and started on magnesium sulfate and Cervidil, and labor was induced. Because of an abnormal fetal heart rate during labor, the patient underwent a Cesarean section. The placenta was very low; therefore, it was cut through to free the baby. There was significant bleeding at this point. Among factor XIII exams, only the clot solubility test was done at that time, showing blood clot present. The patient delivered a boy who weighed 2895 g with Apgar scores of 6 and 6, and the baby was admitted to the neonatal intensive care unit. The patient's estimated blood loss was about 1000 mL.

After the Cesarean section, the patient's oxygen saturation dropped into the 80s, and her creatinine level was becoming elevated. At this point she was given furosemide to maintain adequate perfusion to her kidneys. She was admitted to the intensive care unit to address her increasing creatinine level (175 µmol/L) and oxygen requirements. The patient was also found to have some bleeding through her incision, and thus was put on Cyklokapron 2000 mg bolus intravenously, then 1000 mg intravenously every 8 hours. The bleeding was stopped, the patient's oxygen saturation was normalized and she was discharged to the maternity ward after spending 1 day in the intensive care unit. Her laboratory values, blood pressure, and oxygen saturation were all normalized and she was discharged from the hospital at day 7 after her Cesarean section, without any bleeding complications. The routine coagulation evaluation was in the normal limits. The quantitative assay is not offered in our center.

## Discussion

Cases of factor XIII deficiency have been reported since 1960, when the disorder was first recognized by Duckert et al. [11]. In 1987, only 2 successful pregnancies had been reported in women with congenital factor XIII deficiency treated with substitutive therapy [12]. Some women with factor XIII deficiency have recurrent miscarriages, with no reason for the miscarriages other than the women's factor XIII deficiency.

Subunits A and B of factor XIII (XIII-A and XIII-B) are normally present in mother and fetus during pregnancy. The mother does not experience miscarriage if only the fetus has factor XIII deficiency. Mothers with a deficiency of XIII-A miscarry if they have not received replacement therapy. However, mothers with a deficiency of XIII-B are able to maintain pregnancy. This indicates that it is essential to maintain levels of XIII-A but not XIII-B during pregnancy. In investigations of the implantation period with immunohistochemistry staining, Kobayashi et al. and Asahina et al. showed that XIII-A deficiency is associated with early placental adhesion anomaly and that the local concentration of XIII-A at the placental bed is low in women with this disorder, causing insufficient formation of Nitabuch's layer and the cytotrophoblastic shell [13,14].

Tretten, which is structurally identical to human factor XIII subunit A, is the first recombinant product approved for use in the routine prevention of bleeding in factor XIII-A deficiency. In clinical trials involving a total of 77 patients with congenital factor XIII-A deficiency, Tretten prevented bleeding in 90% of the patients when given monthly [15]. The reported bleeding in our case was likely due to thrombocytopenia as a result of HELLP syndrome. Adverse effects included headache, pain in the extremities, and pain at the injection site. None of the trial participants developed abnormal clots. Tretten is classified as pregnancy Category C (an FDA classification stating that there are no adequate studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). According to the product monograph, it "should be avoided during pregnancy unless the benefits clearly outweigh the risks" [16]. It is also not known whether Tretten can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity.

## Conclusions

To the best of our knowledge, this is the first reported case of a pregnant woman being treated with Tretten. In our patient, this drug, which is not indicated in pregnancy, offered a safe, effective treatment for miscarriages secondary to factor XIII-A deficiency. Further research is required to confirm this finding.

## References:

1. Duckert F: Documentation of the plasma factor XIII deficiency in man. Ann NY Acad Sci, 1972; 202: 190–99
2. Hsieh L, Nugent D: Factor XIII deficiency. Haemophilia, 2008; 14: 1190–200
3. Biswas A, Ivaskevicius V, Thomas A, Oldenburg J: Coagulation factor XIII deficiency. Diagnosis, prevalence and management of inherited and acquired forms. Haemostaseologie, 2014; 34(2): 109–92
4. Dorgalaleh A, Rashidpanah J: Blood coagulation factor XIII and factor XIII deficiency. Blood Reviews, 2016; 30(6): 461–75
5. Fadoo Z, Merchant Q, Abdur Rehman K: New developments in the management of congenital factor XIII deficiency. J Blood Med, 2013; 4: 65–73
6. Abu Rajab Altamani Z, Shaikh R, Omar H et al: Recurrent post tonsillectomy secondary hemorrhage in patients with factor XIII deficiency: A case series and review of literature. Am J Case Rep, 2016; 17: 850–54
7. Dorgalaleh A, Naderi M, Shamsizadeh M: Morbidity and mortality in a large number of Iranian patients with severe congenital factor XIII deficiency. Ann Hematol, 2016; 95(3): 451–55
8. Dorgalaleh A, Tabibian S, Housseini S, Shamsizadeh M: Guidelines for laboratory diagnosis of factor XIII deficiency. Blood Coagul Fibrinolysis, 2016; 27(4): 361–64
9. Kadir RA, Davies J, Winikoff R: Pregnancy complications and obstetric care in women with inherited bleeding disorders. Haemophilia, 2013; 19(Suppl. 4): 1–10
10. Asahina T, Kobayashi T, Takaeuchi K, Kanayama N: Congenital blood coagulation factor XIII deficiency and successful deliveries: A review of the literature. Obstet Gynecol Surv, 2007; 62(4): 255–60
11. Duckert F, Jung E, Shmerling DH: Hitherto undescribed congenital hemorrhagic diathesis probably due to fibrin stabilizing factor deficiency. Thromb Diath Haemorrh, 1960; 5: 176–86
12. Rodeghiero F, Castaman GC, Di Bona E et al: Successful pregnancy in a woman with congenital factor XIII deficiency treated with substitutive therapy. Report of a second case. Blut, 1987; 55(1): 45–48
13. Kobayashi T, Asahina T, Okada Y et al: Studies on the localization of adhesive proteins associated with the development of extravillous cytotrophoblast. Trophoblast Res, 1999; 13: 35–53
14. Asahina T, Kobayashi T, Okada Y et al: Maternal blood coagulation factor XIII is associated with the development of cytotrophoblastic shell. Placenta, 2000; 21: 388–93
15. US Food and Drug Administration: FDA approves Tretten to treat rare genetic clotting disorder. Silver Spring (MD): US Food and Drug Administration, 2014
16. Novo Nordisk Canada Inc.: Product monograph. Schedule D. Tretten. Catridecacog. Recombinant coagulation factor XIII A-subunit. Mississauga (ON): Novo Nordisk Canada Inc., 2014

**Statement**

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