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Cryoprecipitate Meets Congenital Factor XIII Crisis: A Rare Case Report in Pregnancy

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Abstract
Factor XIII deficiency is an extremely rare autosomal recessive bleeding disorder, with an incidence of 1 in 2-3 million live births. It is unique among coagulation factor deficiencies due to its association with recurrent miscarriage, impaired wound healing and life-threatening hemorrhage. Factor XIII (FXIII) is essential for coagulation, wound healing, angiogenesis, and maintenance of hemostatic milieu in pregnancy. Diagnosis often relies on specific FXIII assays as routine tests may be normal. Rarely an acquired deficiency of Factor XIII has been described, that occurs secondary to either hyperconsumption (surgery, DIC, Sepsis, Thrombosis) or hypo-synthesis (liver disease, leukemia) or an immune-mediated process (SLE, RA, Malignancy). *We hereby report a rare case of a pregnant woman with Congenital Factor XIII deficiency managed with cryoprecipitate therapy, who successfully carried her pregnancy to term and delivered a healthy baby. The case highlights the critical role of vigilant antenatal monitoring, timely replacement therapy with multidisciplinary co-ordination.*
Keywords: *Factor XIII deficiency, Cryoprecipitate, Thrombosis, Haemorrhage*

INTRODUCTION:

Factor XIII (FXIII), also known as Fibrin-stabilizing factor or Laki–Lorand factor, is the final enzyme in the coagulation cascade. It plays a critical role in stabilizing the fibrin clot by cross-linking fibrin polymers, thus providing mechanical and biochemical stability to the clot. Unlike other clotting factor deficiencies, FXIII deficiency does not typically alter conventional coagulation screening tests (PT, aPTT), making the diagnosis challenging. Its deficiency predisposes to recurrent pregnancy loss due to impaired placental attachment and stability of maternal-fetal interface, umbilical stump bleeding in neonates, delayed wound healing, intracranial hemorrhage, and intractable surgical bleeding.
Pregnancy has a significant haemostatic change that occurs throughout gestation period where the majority of clotting factors gradually increase. Factor XIII has a two catalytic A-subunits and two carrier B-subunits make up the heterodimer that circulates in plasma as fibrin stabilizing factor (FXIII)/ Laki Lorand Factor/L-L Factor. Numerous physiological and pathological variables can be responsible for variations in FXIII levels [1-4]. Only a few studies, with limited sample sizes, have evaluated changes in FXIII levels throughout pregnancy. The minimum level of FXIII necessary for fetal implantation and preserving hemostasis during pregnancy is uncertain, despite these studies showing a reduction in the hormone during the third trimester. Additionally, it is still unknown what the reference range of FXIII in pregnant women is for the three trimesters of pregnancy [5].
Mutations in 6p15-14 gene cause 'A'subunit deficiency in about 95% of cases and causes prenatal problems like prolonged bleeding and miscarriage. Abortion has been the consequence of all pregnancies complicated by congenital factor XIII (F XIII) deficiency without replacement therapy [6,7].

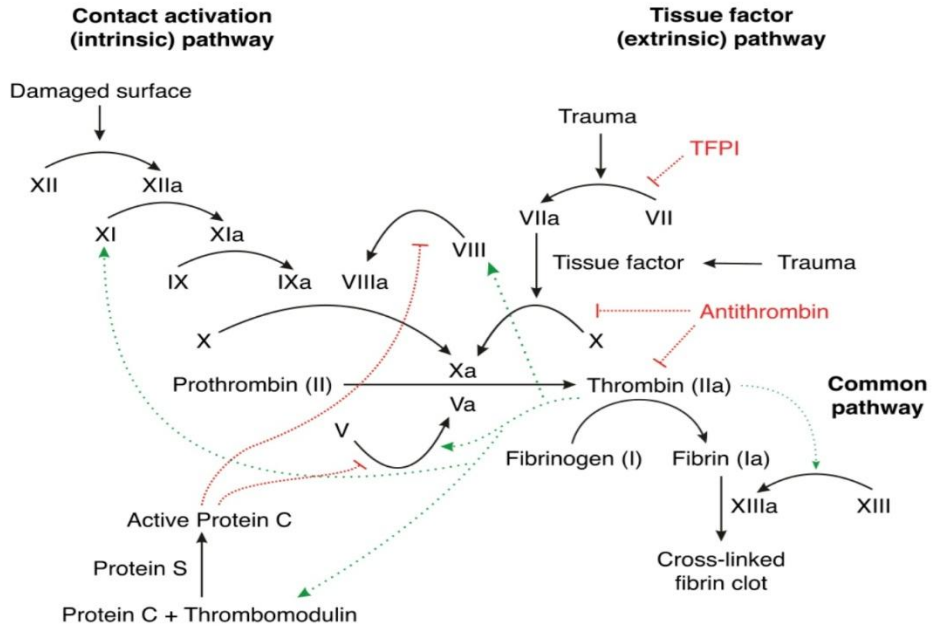

Figure 1 – Clotting Factor Cascade

Case Details:

A 29-year-old G2P1L1 woman, non-consanguineously married, with no history of abortions, known case of epilepsy since childhood with a prevailing Left Parieto occipital Subdural hematoma on treatment presented after her second spontaneous conception with reliable dating. She was booked with us since 7 weeks of gestation.

Obstetric History - First Trimester:

Patient was on Tab. Sodium Valproate 200 mg BD**,** the medication was discontinued at 7 weeks of gestation due to concerns regarding teratogenicity and was subsequently switched to Tab. Levipil 500 mg BD. Patient's last menstrual period (LMP) was on 20th January 2023, and her estimated due date (EDD) was calculated as 27th October 2023, based on menstrual history and confirmed by an early dating scan. Dating scan further revealed a subchorionic hemorrhage measuring 1.9 × 0.6 cm. The nuchal translucency (NT) scan showed a measurement of 2 mm, and first trimester screening (FTS) indicated a low risk for aneuploidy. Mean uterine artery Doppler demonstrated high resistance, with a raised Pulsatility Index for which the patient was started on Tab. Aspirin 150 mg at bedtime after consulting with the hematologist. A Factor XIII antigen assay done at 13 weeks of gestation revealed a 0% antigen level, and cryoprecipitate transfusions were initiated at a dose of 5 units/kg once every 3 weeks. She was also compliant with folic acid supplementation at a dosa of 5mg/day. In view of maternal Factor XIII deficiency, perinatology counselling was obtained, and postnatal evaluation of the neonate was advised.

Second Trimester:

In the second trimester, the patient perceived quickening in the 5th month of amenorrhea. An anomaly scan was performed, which revealed no structural abnormalities, and a fetal echocardiography done at 16 weeks showed cardiac evaluation was normal. She received two doses of Inj.Tetanus Toxoid 2 months apart as a part of routine antenatal immunization. The patient remained compliant with iron and calcium supplementation and continued to receive cryoprecipitate transfusions every 3 weeks at a dose of 5 units/kg. There were no complications, with no history of elevated blood pressure or abnormal oral glucose tolerance test (OGTT), pain abdomen, bleeding, or leaking per vaginum. Ultrasound Abdomen and Pelvis done showed Liver normal in size - 14.6 cm, with coarsened echotexture and nodular surface. The left lobe of liver and caudate lobe appears hypertrophied with no visible focal lesions. The intrahepatic biliary radicles and the common bile duct appeared normal .The portal vein appeared to be replaced by portal cavernoma formation. Few periportal collaterals were also seen. Hepatic veins were normal. She was under regular multidisciplinary follow-up with a neurologist, hematologist, and surgical gastroenterologist throughout this period.

Third Trimester:

In the third trimester, the patient perceived fetal movements well. Growth scan at 28 weeks showed satisfactory fetal growth, and she continued iron and calcium supplementation. She received a total of 12 units of cryoprecipitate up to 36 weeks of gestation, adherent with the established schedule. In view of her previous preterm lower segment cesarean section (LSCS), she was planned for an elective LSCS at 37 weeks of gestation.

Table 1: Investigatory Panel

4/5/23	**7/7/23**	**20/9/23**	**6/10/23**	**16/10/23**	**28/10/23**	**30/10/23**
Hb- 10.1	Hb- 9.8	Hb-10.4	Hb- 10.8	Hb- 10.4	Hb-9.5	Hb- 10.1
PT/INR-12.4/ 1.04	PT/INR- 12.1/ 1.06	PT/INR- 12.4/ 1.02	PT/INR- 12/1	PT/INR- 12.2/1.06	PT/INR- 12.4/1.08	
PTT- 22.8	PTT- 25.4	PTT- 22.6	PTT- 23.4	PTT- 25.6	PTT- 25.8	
PLT-2.76	PLT- 3.14	PLT-2.4	PLT- 3.6	PLT- 2.7	PLT- 3.2	
SGOT/PT- 28/14	SGOT/PT- 24/16			SGOT/PT- 25/18	SGOT/PT- 26/14	
T.BRB-0.96	T.BRB- 0.87			T.BRB-0.77	T.BRB-0.9	
BUN-6 CREAT-0.5	BUN-8 CREAT- 0.6			BUN-8 CREAT- 0.8	BUN- 9 CREAT- 0.6	

Medical History:

- The patient is a known case of Congenital Factor XIII Deficiency**,** diagnosed at the age of 15 years at a private hospital in South India, following a history of prolonged bleeding after application of cast for a right forearm injury. She is a Known case of Epilepsy since childhood, last episode was a month ago before 2nd conception, on Tab. Levipil 500mg BD.
- Known case of Chronic Extrahepatic Portal Vein Obstruction, following Acute thrombosis of portal vein in late 2018 which succumbed her to splenic rupture. Splenectomy done in November 2018 . Post splenectomy, patient was on Tab. Penicillin 250mg BD for a year. Pneumococcal vaccine administered to prevent OPSI. Patient was diagnosed to have Acute Pancreatitis in December 2018, managed medically.
- History of epilepsy with trauma to the head in 2021 after which she developed Intracranial bleeds, was on a serial CT Brain monitoring, transfused 22 units of cryoprecipitate in a month for Left parieto occipital subdural hematoma, which remains under the care of a neurologist with regular follow-up
- Patient had received Recombinant Factor XIII replacement (Tretten XIII-A) once in 2021(CMC Vellore).

During the current pregnancy, she was managed with **cryoprecipitate transfusions every 3 weeks** to maintain adequate clotting function.

Family history- Elder brother is a carrier of factor XIII deficiency- 47% (mild variant). Haven't presented with altered blood parameters or with clinical features.

- **Parents – Third degree consanguineous marriage.**
- Menstrual History- Attained Menarche at 15 years of age. Regular menstrual cycles- 4/30 days, changes 2-3 pads per day, not associated with clots or dysmenorrhea.
- Marital history – Married for 7 years, Non-consanguineous marriage.
- Past Obstetric history – 2017- P1L1- Underwent Emergency LSCS done at 38weeks+3 days in view of transverse lie in labor, severe atonic postpoartum haemorrhage, managed with 8 units of cryoprecipitate transfusion. Patient had MRSA infection postoperatively, medically managed. Baby details: girl baby- 2.20kg-6years-alive and healthy. Evaluated postnatally, bleeding disorders ruled out. Attained developmental milestones at an appropriate age, has an average scholastic performance.

- **No history of spontaneous/missed miscarriage.**

PEDIGREE ANALYSIS OF THE FAMILY

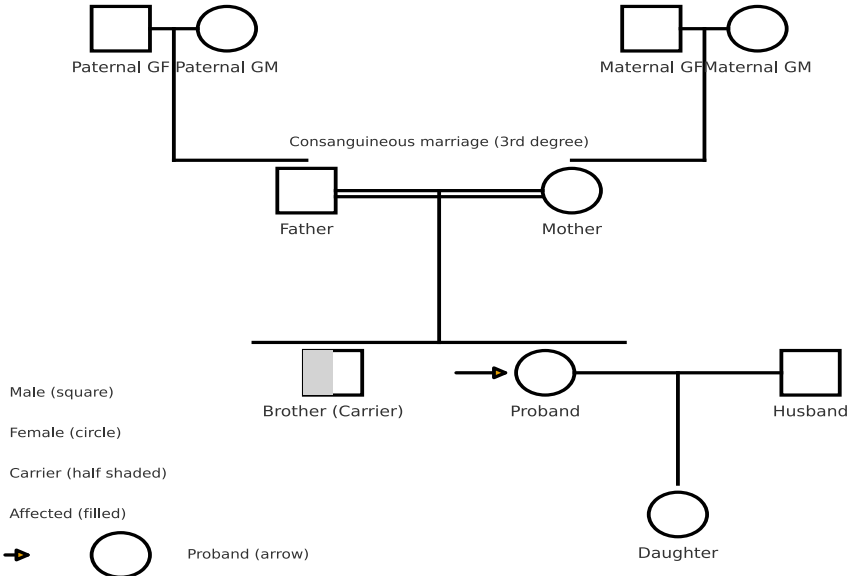

Figure 2: Pedigree Analysis

Postoperative Course:

Patient had a planned Elective LSCS in view of breech presentation at 37 weeks under GA, delivered a girl who weighed 2990g with a APGAR of 7 and 9. Cord ABG: pH-7.339, Lactate- 1.55. Intraoperative findings- LUS was thinned out. Blood loss of 1400ml noted. 6 units of cryoprecipitate transfused on table following which hemostasis was secured. T.Misoprostol 800mcg kept intracavitarily. Bilateral tubes and ovaries were normal. Bilateral tubal sterilization done by Modified Pomeroy's technique. Left Intraperitoneal drain was placed. Patient was shifted to Critical care ICU for observation. Postoperatively on POD1, IP drain collection was 650ml.

Figure 3 – Hematuria on POD2

- Patient developed hematuria on POD2. Renal function tests was done, were within normal limits. 10 units of cryoprecipitate, 1 unit PRBC were transfused postoperatively. Postoperatively repeated levels were **Hb-9.5g/dl, Factor XIII levels- 33%.** Dressing was moderately soaked, removed and reapplied. No active site of ooze noted. Drain site swab taken, revealed growth of Coagulase Negative Staphylococcus. Patient was started on T. Linezolid 600mg BD. On POD3, patient resumed normal bowel and bladder habits, stepped down from ICU. Wound found be healthy. Hematologist review obtained, advised to transfuse 10 units of cryoprecipitate every 3 weeks from 6/11/23, followed up with the same.

DISCUSSION

Factor XIII (FXIII) deficiency, initially described by Duckert et al. in 1960 as a deficit in fibrin-stabilizing factor, remains a rare but clinically significant bleeding disorder [8]. While consanguinity is a known contributing factor, non-consanguineous families have been shown to exhibit a higher prevalence of compound heterozygosity [2]. The diagnosis of FXIII deficiency often hinges on a high index of clinical

suspicion, as standard coagulation profiles—including platelet count, fibrinogen level, bleeding time, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT)—typically remain within normal limits. Therefore, specialized investigations such as FXIII activity assays (quantitative functional testing), clot solubility tests (positive only at very low FXIII activity levels <1–3%), and FXIII antigen assays are essential components of the diagnostic workup [9].

In women, severe FXIII deficiency is frequently associated with menorrhagia, postpartum hemorrhage, and recurrent pregnancy loss. As such, management of pregnancy in these patients demands a multidisciplinary approach, tailored to the individual's bleeding phenotype [10].

Therapy	Advantages	Limitations
Cryoprecipitate	Widely available, inexpensive, contains FXIII 15-33%	Variable concentration, infection risk, volume overload
Plasma-derived concentrate (Fibrogammin)	Standardized dosing, effective prophylaxis	Limited availability in many countries
Recombinant FXIII (Tretten)	High purity, long half-life, once monthly dosing	Expensive, not available in resource-limited settings

Table 2. Comparison of treatment options for Factor XIII deficiency

In the present case, the patient was identified to have undetectable FXIII antigen levels (0%) at 13 weeks of gestation. Given the unavailability of FXIII concentrate, she was managed with cryoprecipitate transfusions (5 units/kg) every three weeks, initiated during the second trimester. Cryoprecipitate, derived from fresh frozen plasma by slow thawing at 1–10°C, is rich in fibrinogen, factor VIII (AHF), von Willebrand factor, and factor XIII. Although originally introduced by Pool et al. over five decades ago as a treatment for hemophilia A [11,12], cryoprecipitate remains a viable alternative in resource-limited settings for managing FXIII deficiency during pregnancy.

Table 3: Studies Evaluating Cryoprecipitate Therapy in Obstetric/Perinatal Settings

Article Number	Citation (Title, Journal, Year, Volume(Issue): Pages)	Study Design / Population	Intervention / Comparator	Key Outcomes & Notes
15	Athulya Shajan et al. "Afibrinogenemia Diagnosed During Pregnancy Successfully Managed with Targeted Cryoprecipitate Transfusion: A Case Report." Journal of Obstetrics and Gynaecology of India. 2021; 71(2): 191–196 PubMed	Case report – a 24-year-old pregnant woman with newly diagnosed afibrinogenemia	Targeted cryoprecipitate transfusion to maintain fibrinogen 50–100 mg/dL	Safe & effective to sustain pregnancy; successful induced vaginal delivery at 34 weeks; fibrinogen maintained postpartum PubMedPMC
16	Xiyu Pan et al. "Association of Adverse Perinatal Outcomes with Blood Components Transfusion in Patients with Acute Fatty Liver of Pregnancy." International Journal of Women's Health. 2025; 17: 21–32 PubMedPMC	Retrospective cohort; 146 mothers (172 fetuses) with acute fatty liver of pregnancy	Blood component transfusion (including cryoprecipitate) vs none	

A comparative analysis of cryoprecipitate use across various bleeding disorders, including FXIII deficiency, is presented in Table 3, underscoring its versatility and continued clinical relevance where recombinant or plasma-derived FXIII concentrates are not readily available.

Recent evidence supports the role of cryoprecipitate in reducing the need for red blood cell transfusions, surgical interventions, and ICU admissions in cases of severe postpartum hemorrhage (PPH), when administered at any stage of bleeding [13]. A similar case report highlighted a pregnant woman with FXIII deficiency who received cryoprecipitate every two weeks as prophylaxis. Although she had a successful vaginal delivery, significant postpartum hemorrhage necessitated additional cryoprecipitate, fresh frozen plasma (FFP), and packed red blood cells, emphasizing the continued bleeding risk associated with delivery in such patients despite prophylaxis [14].

CONCLUSION:

Unlike patients with factor XIII deficiency presenting with recurrent miscarriage, our patient didn't have such history due to the regular cryoprecipitate transfusion.

With watchful monitoring, initiating replacement therapy from 1st trimester, regular follow-ups and optimal usage of cryoprecipitate, we were able to offer the patient, a good antenatal course without pregnancy related complications as well a good perinatal outcome.

A Multidisciplinary team with surgical expertise has promisingly made this possible despite life-threatening bleeding episodes and subsequent neurological morbidities and mortality. Greater research is still warranted in identifying novel approaches to manage this condition.

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