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CASE REPORT

Management of congenital dysfibrinogenemia in pregnancy: A challenging patient case

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Abstract

Afibrinogenemia and congenital dysfibrinogenemia (CD) are rare conditions with limited information available for appropriate management. Previous case reports have demonstrated the safe and efficacious use of fibrinogen replacement therapy (FRT) as a therapeutic approach to prevent hemorrhage and fetal loss in pregnant women with CD. In this case report, we present a 28-year-old pregnant woman who sought testing for CD given her family history. She denied any current or previous bleeding symptoms. Laboratory testing confirmed the diagnosis of CD. She was treated with FRT and prophylactic anticoagulation starting in her third trimester. She had preterm labor that prompted an urgent cesarean section with FRT support. This case adds to the sparse literature about fibrinogen disorders in pregnancy, and highlights the benefits, safety, and tolerability of FRT and prophylactic anticoagulation in pregnant women with CD. Finally, it emphasizes the importance of a multidisciplinary team approach for an uneventful delivery.

KEYWORDS
afibrinogenemia, congenital, dysfibrinogenemia, fibrinogen, hemorrhage, pregnancy

Essentials

- Congenital dysfibrinogenemia (CD) is a rare but potentially serious condition.
- Pregnant women with CD are at risk for significant hemorrhage, thrombosis, and/or fetal loss.
- Fibrinogen replacement therapy may prevent complications in pregnant patients with CD.
- Management of CD requires a multidisciplinary approach.

1 | INTRODUCTION

Fibrinogen serves an essential role in hemostasis by promoting clot formation, platelet aggregation, and fibrinolysis.[1,2] Fibrinogen is synthesized by hepatocytes and has a normal plasma concentration of 150 to 350 mg/dL. Hereditary defects of fibrinogen are extremely rare and can affect the quantity (hypofibrinogenemia and afibrinogenemia) or the quality (dysfibrinogenemia) of circulating fibrinogen. Pregnant women with congenital afibrinogenemia carry a high risk of first-trimester miscarriage and increased antepartum and/or postpartum hemorrhage (APH/PPH). Women with hypofibrinogenemia and dysfibrinogenemia typically experience less frequent and less severe bleeding, but are at risk for bleeding during pregnancy and surgery.[1,2] In these cases, fibrinogen replacement

therapy (FRT) is often required to prevent hemorrhage or fetal loss. Studies leading to commercial approval of most fibrinogen concentrate (human) (FCh) products excluded pregnant patients. However, these products have been successful in treating cases of fibrinogen disorders in pregnancy. We present a case of a hemorrhage-free childbirth in a pregnant patient with congenital dysfibrinogenemia (CD) who received antepartum and postpartum FRT and prophylactic anticoagulation.

2 | CASE REPORT

A 28-year-old gravida 1, para 0 female at 12 5/7 weeks' gestational age with a past medical history of insulin-dependent diabetes mellitus (IDDM) (White Classification D) presented to the hematology clinic seeking testing for CD. Her brother was diagnosed with CD at age 14 after experiencing excessive internal bleeding after a minor motor vehicle accident. Subsequent genetic testing revealed that our patient and her father also had CD.

Upon obtaining her history, she denied excessive bleeding after finger sticks for glucose monitoring, from any prior sports-related injuries, or during wisdom tooth extraction. She also reported an unremarkable menstrual history, with menarche at age 11 years, with regular frequency, duration (5 days), and light- to moderate-flow menstruation. She reported heavy vaginal bleeding after her first sexual intercourse prompting an emergency room visit. She used oral contraceptives until one year before conception.

Coagulopathy workup revealed hemoglobin of 15 g/dL; activated partial thromboplastin time of 30 seconds; mildly elevated prothrombin time and international normalized ratio of 16.8 and 1.4 seconds, respectively; elevated thrombin time (TT) at 37.3 seconds; and elevated reptilase time (RT) of >100 seconds. Fibrinogen antigen level was mildly elevated at 386 mg/dL, but fibrinogen activity level (FAL) was critically low, at <60 mg/dL, yielding a ratio of <0.16. Thromboelastography results were normal. These results confirmed her suspected diagnosis of CD.

FAL was monitored every other week during her second trimester, with a plan to achieve FAL of 50 to 150 mg/dL, and ≥100 mg/dL during the third trimester to prevent placental abruption. Through the second trimester, FAL remained close to baseline (around 60 mg/dL); thus, no intervention was necessary. At 27 3/7 weeks' gestational age, FAL fell below 60 mg/dL. FRT was then initiated with FCh, and primary cesarean section was planned for 37 weeks to coordinate with a perioperative FAL target of >150 mg/dL, and to ensure the availability of staff in the event of hemorrhage.

FCh doses were calculated on the basis of the patient's actual pregnancy body weight according to the following formula (and rounded to the nearest vial size): [target FAL (mg/dL) – measured FAL (mg/dL)]/1.7(mg/dL per mg/kg body weight).[3] Each FCh vial supplied 1082 mg in 50 mL sterile water for injection, which was filtered using a 15 μm albumin filter and administered over 20 minutes (5 mL/min) using a syringe pump in the outpatient infusion center. FAL was measured immediately before (trough) and approximately one hour after (peak) the completion of each FCh infusion (Figure 1). Throughout FRT, the patient was monitored for signs of anaphylaxis and hypersensitivity. No fetal monitoring was performed during the infusions.

Due to the increased risk for thrombosis in pregnancy, with FRT, and in CD, the patient was initiated on prophylactic anticoagulation at 27 weeks with enoxaparin 40 mg subcutaneously daily. Additionally, antenatal fetal surveillance was ordered to monitor fetal well-being. The patient underwent a weekly fetal nonstress test or biophysical profile. At 32 weeks, testing frequency was increased to twice weekly per standard of care for IDDM. All antenatal testing was normal.

At 35 3/7 weeks, the patient was admitted for preterm labor. A high-dose (4328 mg) FCh infusion was administered due to an admission FAL of 119 mg/dL. This was followed by an urgent cesarean section. The patient was able to receive neuraxial anesthesia, but this is typically avoided due to potential difficulty assuring adequate factor replacement. The surgery was uncomplicated, with a normal estimated blood loss of 700 mL. Placental pathology was unrevealing for thrombosis or any other vascular abnormalities.

On postpartum day (ppd) 1, FAL was noted to be 114 mg/dL, so the patient received an additional FCh infusion to meet the perioperative goal of >150 mg/dL. Prophylactic anticoagulation was also reinitiated on ppd 1 with heparin 5000 units subcutaneously every 8 hours. On ppd 3, the patient remained clinically stable, and there was no concern for abnormally heavy bleeding. Consequently, the FAL target was readjusted to be >100 mg/dL. Heparin was transitioned to enoxaparin 40 mg subcutaneously daily, and FAL remained>100 mg/dL at discharge. The patient returned to the outpatient infusion center on ppd 6 and on ppd 10 to receive FCh infusions since FAL was <100 mg/dL (Figure 1). FRT was subsequently discontinued and eventually FAL returned to baseline (<60 mg/dL). The patient was continued on enoxaparin for a total of 6 weeks postpartum and remained without any signs or symptoms of hemorrhage or thrombosis.

3 | DISCUSSION

Diagnosis of fibrinogen disorders starts with clinical suspicion due to unexplained bleeding, thrombosis, or pregnancy morbidity for which other testing did not uncover a cause, hence why testing for dysfibrinogenemia is often added as a second- or third-line evaluation in these clinical scenarios. TT and RT are primary screening tests to confirm the diagnosis of dysfibrinogenemia. TT measures the rate of fibrin clot formation by thrombin cleaving fibrinopeptide A and B from fibrinogen, resulting in the fibrin monomer and subsequently the fibrin clot.[4] In dysfibrinogenemia, the release of fibrinopeptide A and/or B can be inhibited, or fibrin monomer polymerization may be prevented, thereby prolonging TT. RT differs from TT in that reptilase cleaves only fibrinopeptide B from fibrinogen. If either of these tests is positive, then the ratio of FAL and fibrinogen antigen level should confirm the diagnosis. Values <0.8 to 1.7 correlate to dysfibrinogenemia, as in the present case.[3]

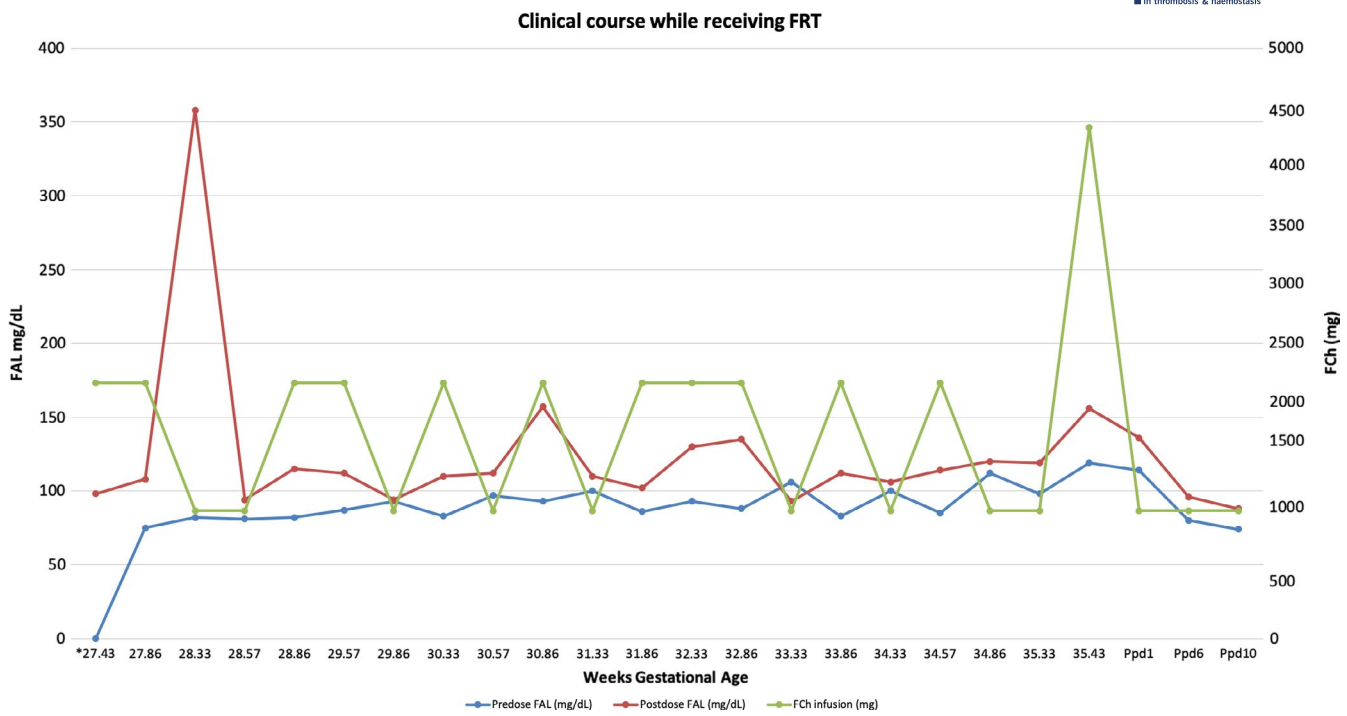

FIGURE 1 Clinical course while receiving FRT (* lower limit of detection is 60 mg/dL). FAL, fibrinogen activity level; FCh, fibrinogen concentrate (human); FRT, fibrinogen replacement therapy

Fibrinogen disorders in pregnancy are associated with APH, PPH, and pregnancy loss, highlighting the importance of fibrinogen as a hemostatic factor and as an adhesive molecule between the placenta and the uterus. In pregnant patients without fibrinogen disorders, the rate of early pregnancy loss in clinically recognized pregnancies is 10%.[5-10] However, in one report of 13 pregnant patients with afibrinogenemia, only five of the pregnancies continued to term, including one that required a cesarean section due to placental abruption. For the remaining pregnancies, seven resulted in spontaneous abortion at 6 to 7 weeks' gestation, and one stillbirth occurred at 27 weeks' gestation subsequent to placental abruption.[9] Similarly, Casini et al[11] reported spontaneous abortion in 19.8% and postpartum hemorrhage in 21.4% of 111 pregnancies in patients with CD. In pregnant women with CD, without FRT, APH usually manifests after week 5 of gestation, with spontaneous abortion occurring between 6 and 8 weeks of gestation.[6] In pregnancies that continue, the fetus is not usually affected, except in cases of severe afibrinogenemia, which can cause intracranial hemorrhage and umbilical bleeding.

Due to the rarity of CD, many management recommendations are only derived from previous case reports and small series focusing on afibrinogenemia. Women with CD can experience pregnancy complications similar to those with afibrinogenemia; however, these patients may not always be identified because CD can be asymptomatic.[8,12,13] In severe cases (FAL <50 to 60 mg/dL), frequent FAL monitoring and FRT is the mainstay of treatment for continuation of the pregnancy and to limit delivery complications, although this is not guaranteed.[14,15] Guidelines and experts have recommended establishing FAL targets between 60 and 100 mg/dL during pregnancy. As the pregnancy progresses and the need for fibrinogen increases, higher doses of FRT may be required; however, endogenous fibrinogen production simultaneously increases, which can help maintain the target FAL. A FAL target of >150 to 200 mg/dL may be necessary during labor and delivery, which may require continuous infusion FRT.[16]

In nonpregnant patients, FCh is a well-tolerated and overall safe method of FRT, as the most commonly observed (>1% of patients) adverse reactions in clinical studies were fever and headache. More serious complications may include transfusion reactions, infection, and thrombosis.[4] CD is also associated with a 20% to 30% lifetime risk of thrombotic events.[11,12] Pregnant patients with CD are already in a hypercoagulable state, and the addition of FRT contributes further to the risk of thrombosis. Therefore, careful investigation of the patient's personal and family history is necessary to determine the most likely phenotype for thrombosis or bleeding, and to ultimately decide whether to incorporate prophylactic anticoagulation into overall management. For our patient, we opted to include prophylactic anticoagulation in her regimen to preserve hemostatic balance as she received aggressive FRT. With the help of a multidisciplinary team, including maternal fetal medicine (MFM), pharmacy, and hematology, our patient was able to have a safe and successful pregnancy and delivery of a viable infant near term.

4 | CONCLUSION

Management of the rare condition of CD in pregnancy is complex, and requires multidisciplinary collaboration between hematology, obstetrics and gynecology, MFM, anesthesia, pharmacy and blood

bank services. Careful assessment of clinical and laboratory factors is of utmost importance to guide treatment. This case adds to the sparse literature about fibrinogen disorders in pregnancy and highlights the benefits, safety, and tolerability of FRT and prophylactic anticoagulation in pregnant women with CD.

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RELATIONSHIP DISCLOSURE

ML is a GSK Speakers Bureau member, a Sanofi Genzyme speaker, and a GSK Advisory Board participant, for which she receives honoraria. The remaining authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

ML provided clinical care for the patient and made substantial contributions to the conception and design, acquisition, analysis, and interpretation of data; drafting of the manuscript; revised the manuscript critically for important intellectual content; and gave final approval of the version to be published. MM provided clinical care for the patient and contributed to the drafting and critical revising of the manuscript for important intellectual content. MC contributed to acquisition and interpretation of data and critically revised the manuscript for important intellectual content. YS and DS contributed to the critical writing and revising of the intellectual content. RB served as primary consultant in the management of the patient, provided clinical care for the patient, made substantial contributions to the conception and design, analysis, and interpretation of data; revised the manuscript critically for important intellectual content; and gave final approval of the version to be published.

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