Received: 13 August 2019 | Revised: 4 December 2019 | Accepted: 5 December 2019

DOI: 10.1002/rth2.12300

CASE REPORT

rpth research & practice in thrombosis & haemostasis

Pregnancy outcome in afibrinogenemia: Are we giving enough fibrinogen concentrate? A case series

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Handling Editor: Pantep Angchaisuksiri

Abstract

Congenital afibrinogenemia is a rare autosomal recessive disorder associated with an increased risk of hemorrhage, thrombosis, and obstetric complications. This case series of 4 pregnancies in 2 related patients seeks to address the key clinical question of the necessary doses of fibrinogen concentrate during pregnancy and puerperium. One pregnancy without the prophylactic use of fibrinogen concentrate resulted in spontaneous abortion. The second pregnancy was complicated by a subchorionic hematoma despite the prophylactic administration of fibrinogen concentrate to maintain the plasma trough levels at ≥0.6 g/L. Labor was complicated by postpartum hemorrhage with a blood loss volume of 1480 cc. Two weeks later, the patient presented with postpartum thrombosis. The other 2 pregnancies were uncomplicated with fibrinogen trough levels ≥1.0 g/L during pregnancy and ≥1.5 g/L during labor. These cases illustrate that during pregnancy, patients may benefit from fibrinogen trough levels ≥1.0 g/L. In addition, the increased risk of postpartum thrombosis with prolonged fibrinogen supplementation warrants personalized postpartum advice that is guided by postpartum blood loss.

KEYWORDS

abortion, afibrinogenemia, blood coagulation disorders, precision medicine, pregnancy, spontaneous

Essentials

- Congenital afibrinogenemia is associated with a high rate of obstetric complications.
- We report 4 pregnancies in 2 related patients with congenital afibrinogenemia.
- Both hemorrhagic and thrombotic complications can occur in patients with afibrinogenemia.
- Maintaining fibrinogen levels ≥1.0 g/L during pregnancy and ≥1.5 g/L during labor may reduce the risk of fetal loss.

1 | INTRODUCTION

Congenital fibrinogen defects can be quantitative (afibrinogenemia or hypofibrinogenemia), qualitative (dysfibrinogenemia), or a combination of both (hypodysfibrinogenemia). Congenital afibrinogenemia (the complete absence of circulating fibrinogen) is an autosomal recessive disorder with a prevalence of 1:1.000.000.[1–3] The disorder typically presents at birth with umbilical cord bleeding.

Other types of frequently occurring bleeding are easy bruising, soft tissue bleeding (spontaneous), muscle and joint bleeding, gastrointestinal bleeding, genitourinary bleeding, and intracranial hemorrhage.[1,3–5] Interestingly, patients with afibrinogenemia may also have an increased risk of thrombosis because they form loosely packed and unstable thrombi with a tendency to embolize.[1,2,5,6] Obstetric complications, such as first-trimester pregnancy loss or antepartum and postpartum hemorrhage (often caused by placental abruption), are also common.[4,6,7] There are no universal guidelines on the optimal trough levels of fibrinogen during each stage of pregnancy to prevent bleeding complications, and treatment is based on expert opinion. Although there is no consensus on the optimal values during pregnancy or in the peripartum period, it is suggested that the fibrinogen level should be maintained at ≥0.5-0.6 g/L during pregnancy and ≥1.0-1.5 g/L during labor.[5,8] The current Dutch national guidelines advise the maintenance of fibrinogen levels at ≥0.6 g/L during pregnancy and ≥1.0 g/L during labor.[9] We address the key clinical question of the optimal doses of fibrinogen concentrate during pregnancy and puerperium, by presenting the clinical outcomes of 4 pregnancies in 2 related women with congenital afibrinogenemia. All patients provided written informed consent for publication of this case series.

2 | CASE SERIES DESCRIPTION

The first pregnancy occurred in a 27 year-old woman. She was diagnosed with afibrinogenemia at 7 years of age after a large hematoma formed on her buttocks and upper legs after playing on a seesaw, with a fibrinogen level <0.3 g/L. She had a homozygous nonsense mutation resulting in a STOP codon in the *FGA* gene (c.1001G > A, p.Trp334*).[10] Both parents were carriers of the mutation and had no history of abnormal bleeding or thrombosis. There was no consanguinity in the family. She was treated with on-demand fibrinogen concentrate from the time of diagnosis. During her first pregnancy, the patient planned a visit to the outpatient clinic to discuss her pregnancy. However, before the visit took place, she was admitted to the hospital at 13 weeks of pregnancy with subchorionic bleeding. She received 2 g (33 mg/kg) of fibrinogen concentrate on admission followed by the continuous infusion of 4 g (67 mg/kg) of fibrinogen every 24 hours. However, 3 days after admission, ultrasound examination showed the loss of the fetal heartbeat, and a spontaneous miscarriage occurred. She had a dilation and curettage procedure in the operating room due to heavy blood loss. The total blood loss volume was 1100 cc and she received 2 units of packed red blood cells.

A year later, the patient became pregnant again, and prophylactic treatment with fibrinogen concentrate was started immediately, maintaining a target fibrinogen level ≥0.6 g/L. She received 3 g (50 mg/kg) of fibrinogen concentrate once every 4 days. Despite the prophylactic regimen, she experienced a subchorionic bleeding at 15 weeks of pregnancy with a fibrinogen level of 0.7 g/L. Her target level of fibrinogen was raised to ≥1.0 g/L; to achieve this level, she required 3 g of fibrinogen concentrate every other day. At 29 + 1 weeks, the patient was readmitted to the hospital because of a threatened abortion with symptomatic cervix shortening of 11 mm. She had abdominal pain and dark blood loss. Corticosteroids were given to stimulate fetal lung maturation. Her symptoms disappeared, and she was able to leave the hospital 3 days later. At 40 + 1 weeks, she went into labor and received 1 g (17 mg/kg) of tranexamic acid and 2 g (33 mg/kg) of fibrinogen concentrate to maintain a target level ≥1.0 g/L. Labor progressed uneventfully, and she vaginally delivered a healthy girl. However, a couple of hours later, a heavy bleeding occurred, and she received oxytocin, misoprostol, and tranexamic acid for postpartum hemorrhage. Her fibrinogen level at that time was 1.0 g/L, and 2 g (33 mg/kg) of fibrinogen concentrate was given to control the bleeding. The total blood loss volume was 1480 cc, and she was discharged 2 days later. She continued fibrinogen concentrate infusions of 3 g (50 mg/kg) every 3 days until 1 week after labor and continued tranexamic acid (1 g [17 mg/kg] every 8 hours) because of mild vaginal blood loss. Two weeks postpartum, she presented at the hospital with a thrombosis of the gastrocnemius vein and thrombophlebitis of the long saphenous vein in her left leg. Tranexamic acid treatment was stopped, and she was treated with acetylsalicylic acid for 6 weeks with good clinical results.

The third pregnancy described in this series occurred in a 32-year-old second cousin of the previously described woman, only a few weeks apart from the above-mentioned pregnancy (Figure 1A). She was diagnosed with afibrinogenemia at birth due to umbilical cord bleeding, with a fibrinogen level <0.2 g/L. She had the same homozygous mutation in the *FGA* gene. A simplified family tree is shown in Figure 1B. The genotypes, laboratory values, and clinical phenotypes of the patients and family members are shown in Table 1. The couple was counseled, and the partner had a normal fibrinogen level. In the initial stage of the first trimester, the target fibrinogen level was maintained at ≥0.6 g/L. However, this level was raised to ≥1.0 g/L after her cousin's complicating event with subchorionic bleeding at 15 weeks. This target fibrinogen level was reached by the administration of 3 g (44 mg/kg) of fibrinogen concentrate every other day. During labor, the target fibrinogen level was set at ≥1.5 g/L. She gave birth to a healthy daughter at 39 + 1 weeks by vaginal delivery after an uneventful pregnancy and labor. The target fibrinogen level was reached with 1 bolus of 3 g (44 mg/kg) of fibrinogen concentrate at the time of maximal dilation. She did not receive tranexamic acid during labor or in the postpartum period.

Two years later, the second patient was pregnant again. Her initial target levels were ≥0.6 g/L during the first 12 weeks of pregnancy and ≥1.0 g/L during the second and third trimesters. She received 2 g (29 mg/kg) of fibrinogen concentrate every other day, which was raised to 3 g (44 mg/kg) every other day at 22 weeks to reach the target levels. At 11 weeks, she forgot to administer a dose of fibrinogen concentrate. This dose was administered 1 day later. However, she experienced vaginal bleeding the next day at a trough level of 1.15 g/L. Evaluation by vaginal ultrasound showed no abnormalities. Trough levels were maintained above 1.0 g/L with the administration of 3 g (44 mg/kg) of fibrinogen concentrate every other day, and the rest of the pregnancy progressed uneventfully. She gave birth to a healthy daughter at 39 + 3 weeks of pregnancy by vaginal delivery, with a fibrinogen level ≥1.5 g/L during labor. Replacement therapy was stopped 4 days postpartum in the absence of vaginal blood loss.

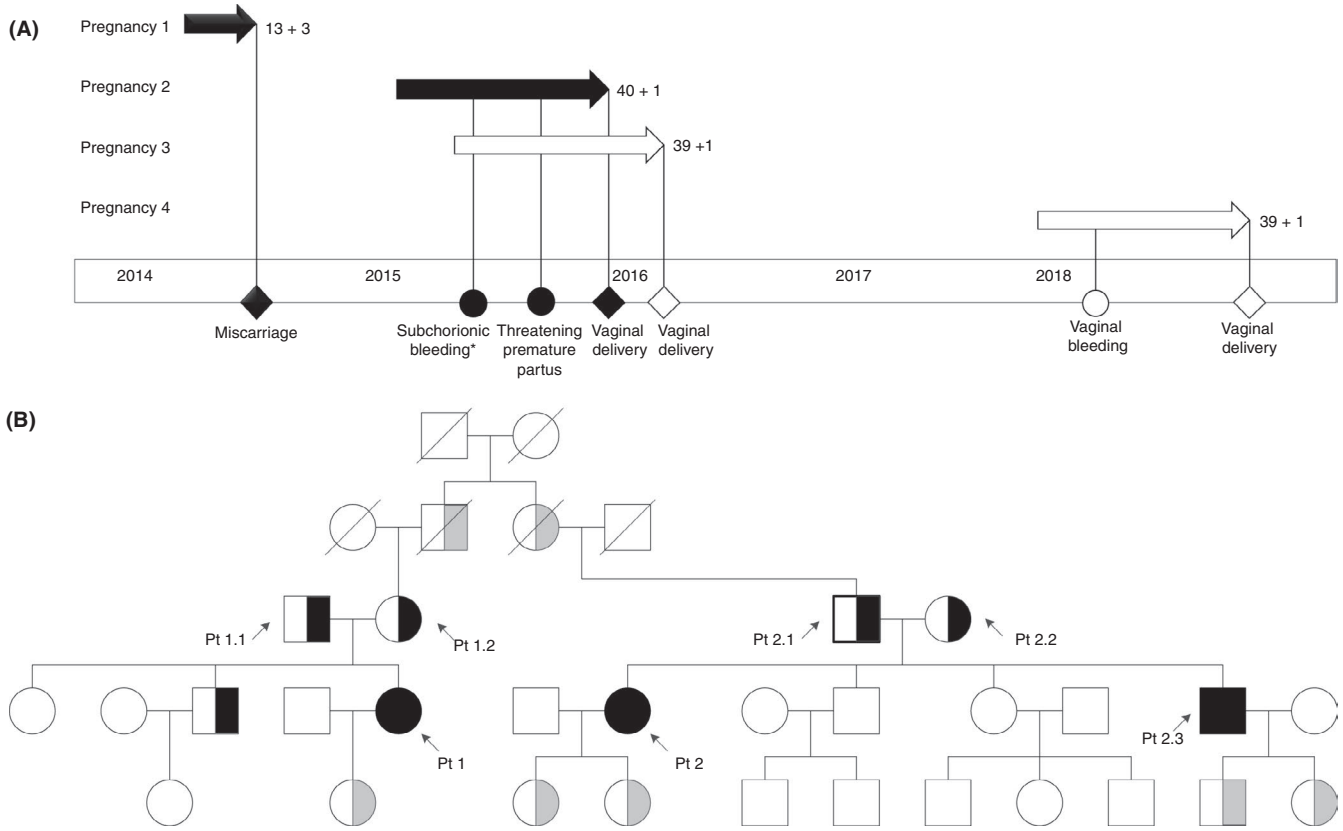

FIGURE 1 (A) Timeline of described pregnancies. Black = patient 1, white = patient 2, *in response to this, target fibrinogen levels were raised to ≥1.0 g/l for both patients, (B) Family tree. Grey = unconfirmed carrier

TABLE 1 Genotypes, laboratory values, and clinical phenotypes of the patients and their family members

Patient	Genotype FGA c.1001G > A p.Trp334*	PT (s)	APTT (s)	Fibrinogen antigen (g/L)	Fibrinogen activity (g/L)	Clinical phenotype	ISTH BAT
1	Homozygous	>100	>200	0.25	0.20	Bruising, muscle bleeds, traumatic joint bleeds, miscarriage requiring red blood cell transfusion, postpartum hemorrhage	17
1.1	Heterozygous	NA	NA	2.0	1.9	None	0
1.2	Heterozygous	NA	NA	1.8	1.7	None, no miscarriages, 3 successful births without complications	0
2	Homozygous	58	46	0.24	0.18	Umbilical stump bleeding at birth, bruising, prolonged wound healing, muscle bleeds, traumatic joint bleeds, red blood cell transfusion after skiing accident	17
2.1	Heterozygous	14	31	NA	2.77	None	0
2.2	Heterozygous	14	28	NA	2.40	Epistaxis, menorrhagia, 1 miscarriage, 4 successful births without complications	4
2.3	Homozygous	99	238	0.38	<0.5	Bruising, muscle bleeds, plasma transfusion after car accident	12

Note: Patient numbers correspond to the associated number in the family tree in Figure 1B.
APTT, activated partial thromboplastin time; BAT, Bleeding Assessment Tool; NA: not available; PT, prothrombin time.

3 | DISCUSSION

These cases illustrate the difficulties faced when treating women with congenital afibrinogenemia, who experience an increased risk of both hemorrhage and thrombosis during pregnancy and in the peripartum period. Large-scale studies on this topic do not exist, but most guidelines, including the Dutch national guidelines, currently advise the maintenance of fibrinogen levels at ≥0.6 g/L during pregnancy

to prevent fetal loss; this level is based on expert opinion and case reports.[8,11–16] Interestingly, although the target level was reached during the second pregnancy, bleeding complications still occurred.

In the second patient, a fibrinogen trough level was established and maintained at ≥1.0 g/L, and no complications were reported during her 2 pregnancies. The spontaneous vaginal bleeding observed after missing 1 dose of prophylactic fibrinogen concentrate suggests that she might have had more complications if lower trough levels had been targeted.

In addition, women with afibrinogenemia and hypofibrinogenemia are at risk of thrombotic events during the puerperium, as observed in our first patient. This risk may or may not be related to fibrinogen replacement therapy.[5,6,17] Although thrombotic events have been described in relation to high-dose fibrinogen concentrate therapy, it is also possible that adequate fibrinogen replacement in patients with afibrinogenemia decreases the prothrombotic risk by providing fibrinogen as a ligand to trap increased levels of circulating thrombin and control the disrupted thrombin regulation.[11] Antifibrinolytic drugs can be used in patients with afibrinogenemia, but data are scarce and controversial.[11,12] The thrombotic event in our first patient may have been related to the combination of her afibrinogenemia and the use of fibrinogen concentrate and tranexamic acid. The main contributing factor remains uncertain. Therefore, the postpartum administration of fibrinogen concentrate and antifibrinolytic agents should be used with caution and stopped as soon as possible. To optimize the treatment of pregnant women with afibrinogenemia, an individualized peri- and postpartum plan with documented target trough levels of fibrinogen should be made. Prophylactic therapy should be adjusted based on the clinical phenotype. In the absence of an absolute indication, cesarean section is not recommended in these patients, as this procedure may increase the risk of postpartum thrombosis.[12]

Based on our case series, we suggest maintaining plasma fibrinogen concentrations at ≥1.0 g/L during pregnancy, starting immediately after the pregnancy is discovered, and at ≥1.5 g/L during labor. The medical history of the patient and the family history can be used as guidance when creating a personalized treatment plan with preset trough levels, based on the occurrence of thrombotic or bleeding events. In the puerperium, the supplementation with fibrinogen concentrate and the use of antifibrinolytic agents should be based on the amount of blood lost and stopped early to reduce the risk of thrombosis due to the postpartum period and immobilization.

RELATIONSHIP DISCLOSURES

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

JLS collected and interpreted the clinical data and wrote the manuscript. BAPL-vG, MC and SEMS treated the patients, critically reviewed the manuscript, and gave final approval.

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How to cite this article: Saes JL, Laros-van Gorkom BAP, Coppens M, Schols SEM. Pregnancy outcome in afibrinogenemia: Are we giving enough fibrinogen concentrate? A case series. *Res Pract Thromb Haemost*. 2020;4:343–346. https://doi.org/10.1002/rth2.12300