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REVIEW ARTICLE

Fibrinogen replacement therapy for congenital fibrinogen deficiency

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Summary. This review of published studies was conducted to derive data on patients with congenital fibrinogen deficiency (CFD), including dosing of fibrinogen replacement therapy, outcome, and adverse events, either temporally related or distant to fibrinogen replacement, in order to assist clinicians in developing treatment plans for patients with CFD. A systematic review was performed of case reports identified by a MEDLINE search between 1961 and 2010. Eligible studies included subjects with a diagnosis of CFD who received fibrinogen replacement. An attempt was made to extract dose, frequency, duration, hemostatic efficacy and adverse events such as thrombosis or allergic reactions. Reported thrombotic events distant from fibrinogen replacement were also recorded. From 104 papers reviewed, a total of 50 cases were identified: afibrinogenemia (35), hypofibrinogenemia (6), and dysfibrinogenemia (9). Fibrinogen replacement therapy was generally effective in preventing or treating bleeding in doses adequate to achieve and maintain fibrinogen activity above 50–100 mg dL^{-1} (non-surgical and obstetric use) or 100–200 mg dL^{-1} (surgical prophylaxis). Increased fibrinogen clearance was observed with massive hemorrhage, major surgery, and advanced pregnancy. Obstetric outcomes were optimized when fibrinogen replacement was initiated prior to conception. Uncontrolled hemorrhage, allergic reactions and antibody formation were rare events. However, thromboses, both related and unrelated to fibrinogen replacement, occurred in 15 of 50 (30%) patients overall, and in eight of 12 (67%) adult non-obstetric patients with afibrinogenemia. Published fibrinogen replacement regimens are presented for 50 CFD patients. Fibrinogen replacement therapy requires careful monitoring of fibrinogen levels. Afibrinogenemia is associated with thromboembolic complications with or without treatment.

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Introduction

Fibrinogen plays a pivotal role in normal hemostasis by promoting clot formation, platelet aggregation, and fibrinolysis [1–3]. Fibrinogen is a 340-kDa protein synthesized primarily by hepatocytes. Normal plasma fibrinogen concentrations typically range from 150 to 350 mg dL^{-1}, with a half-life of approximately 3 days [4]. Hereditary defects of fibrinogen can affect either the quantity (hypofibrinogenemia and afibrinogenemia) or the quality (dysfibrinogenemia) of circulating fibrinogen.

Bleeding secondary to afibrinogenemia typically presents in the neonatal period, with up to 85% of cases manifesting umbilical cord bleeding [2]. Bleeding can occur in the skin, soft tissues, muscles, joints, gastrointestinal tract, or genitourinary tract, with intracranial hemorrhage (ICH) being a major cause of death [2,3]. Moreover, first-trimester abortion occurs commonly in afibrinogenemia. Afibrinogenemic women may also experience antepartum and postpartum hemorrhage, particularly placental abruption. Patients with hypofibrinogenemia and dysfibrinogenemia typically experience less frequent and less severe bleeding events, but are at risk for hemorrhage related to pregnancy and surgery [2,3].

Treatment for congenital fibrinogen deficiency (CFD) consists of replacement with fresh frozen plasma (FFP), cryoprecipitate (Cryo), or fibrinogen concentrate (FC). The therapeutic goal is to achieve a plasma fibrinogen activity level of 100–150 mg dL^{-1} [4]. The use of FFP and Cryo has declined, because of concerns related to transfusion-associated complications. FFP carries a risk of volume overload as well as acute lung injury (transfusion-related acute lung injury [TRALI]), a serious and potentially fatal complication. FFP and Cryo are further limited by: the infusion of large amounts of unnecessary plasma proteins, including all plasma proteins in FFP, and fibronectin, von Willebrand factor, factor VIII, FXIII and α-macroglobulins in Cryo; anaphylatoxins that may

trigger allergic reactions; and the need to thaw FFP and Cryo before use. In addition, thrombosis has been reported with fibrinogen replacement therapy (FRT); however, whether and to what degree treatment increases the risk of thrombosis in CFD remains an open question.

Four human plasma-derived, viral-inactivated FCs are available worldwide, but only one is approved for use in the USA (Table 1). Although plasma derivatives can never be completely free of the risk of viral contamination, manufacture of these products incorporates rigorous safety testing of the source plasma, and further pathogen elimination processes. Clinical studies have shown that FC has a very low risk of treatment-related pathogen transmission [5].

The objective of this review was to provide information on FRT, including dose, dose frequency, duration, hemostatic efficacy and adverse events, by CFD type (afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia), population (adult, pediatric, and neonate), and clinical indication (prevention and treatment of bleeding, use around the time of pregnancy, and prevention of surgical bleeding). Although the objective was not to explore thrombosis in CFD in general, it became necessary to place evidence for recent and old thrombosis within the context of the individual patient bleeding and treatment history.

Methods

Data sources

A systematic search for publications was performed using MEDLINE from 1961 to 2009. Searches included the following terms: 'clinical studies', 'congenital fibrinogen deficiency', 'afibrinogenemia', 'hypofibrinogenemia', 'dysfibrinogenemia', 'fibrinogen concentrate', 'cryoprecipitate', 'fresh frozen plasma', 'pregnancy', 'bleeding', and 'surgery'. The authors screened each study and decided which ones met the selection criteria.

Selection criteria

Selection criteria included: (i) subjects with a diagnosis of CFD; (ii) FRT on at least one occasion; and (iii) information on treatment indication, dosing or level achieved, and outcome.

Two authors reviewed all of the papers identified, and independently confirmed eligibility and pertinent data. For consistency of comparison, an attempt was made to translate doses into dose per kilogram in cases where patient weight was recorded. For the obstetric cases, dose per kilogram was based upon prepregnancy weight, where given. Pediatric dosing was estimated from the 50th percentile weight for age in children under the age of 3 years, as variation of weight with age is relatively small in young children.

Results

Study search results

The search identified a total of 104 articles, of which 42 contained descriptions of FRT in 50 congenitally deficient patients judged adequate for inclusion. The 50 patients received FC, Cryo and FFP in a total of 35, 18 and six cases, respectively, with nine patients receiving more than one type of FRT.

Prevention or treatment of hemorrhage

Patient characteristics included: (i) afibrinogenemia in 20, and hypofibrinogenemia in 2 – seven adults, 13 children, and two neonates; (ii) 13 females, and nine males; (iii) five treatment courses for ICH; (iv) two courses for prophylaxis of toddlers while they were achieving stable walking skills; and (v) two courses to support antithrombotic therapy for initial presentations with ischemic arterial occlusive lesions and/or pulmonary emboli (Table 2). Treatment characteristics included FC in 14 cases, Cryo in 10, and FFP in two.

Initial dosing for life-threatening hemorrhages was approximately 100 mg kg^{-1}, but was 300 mg kg^{-1} in one infant [6]. Adults were treated with 3–4 g of FC (approximately 50 mg kg^{-1}) given every 2–4 days. Treatment courses for life-threatening hemorrhages were usually monitored, and plasma fibrinogen concentration was generally maintained above a targeted trough level of 100 mg dL^{-1} during the initial replacement course. Two infants with ICH required 100 mg kg^{-1} every 5 days and 230 mg kg^{-1} weekly to maintain a trough of 100 mg dL^{-1} [7,8]. Toddlers on prophylaxis were

Table 1 Fibrinogen factor concentrates

Brand	Company/Site of manufacture	Plasma source	Fractionation	Viral inactivation
Clottagen®	LFB/France	Western Europe; unpaid	Adsorption on aluminum hydroxide gel Ion exchange chromatography and affinity chromatography	TNBP/polysorbate 80
Fibrinogen HT	Benesis/Japan	Japan; unpaid	Ethanol fractionation, glycine precipitation	TNBP/polysorbate 80; dry heat, 60 °C, 72 h; 35-nm nanofiltration
Fibroraas®	Shanghai RAAS	China; paid and unpaid	Multiple fractionation	TNBP/polysorbate 80
Haemocomplettan® P	CSL Behring	USA, Austria, Germany; paid and unpaid	Multiple precipitation	Heat-treated at 60 °C, 20 h
RiaSTAP® (USA)				

TNBP, tri(n-butyl) phosphate.

Table 2 Dosing and outcome of fibrinogen replacement for prevention or treatment of spontaneous or traumatic bleeding

Author, year, reference	CFD type	Treatment indication	Sex	Age	Fibrinogen source and relevant concomitant medications	Dose/dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Adult (≥ 18 years of age)									
MacKinnon, 1971 [14] See similar case in Table 4, Dupuy (2001)	Afib	Bruising, menorrhagia, hemarthroses	F	36 years	FC OCP	3 U every 4 weeks	NA	Death from ICH	At postmortem, thoracic and abdominal aortic narrowing, diffuse arteriolosclerosis, embolic lesions to toes, left internal carotid, vertebral, and subclavian artery occlusion; whether related to treatment or spontaneous unknown
Matsumoto, 2008 [9]	Afib < 5 mg dL^{-1}	Right cerebral, subcortical hemorrhage Right thalamic hemorrhage at 47 days Increased FDP and DD at 57 days; IVC thrombus and PE at 72 days Total of seven recurrent ICH episodes	F	35 years	FC FC UFH 833 U h^{-1} IV days 72–86; 12 500 U SC twice daily days 86–100; warfarin 2–3 mg day^{-1}	8 g initially, and then 2 g every 2 days for 26 days 3–4 g every 2 days from days 47 to 100 based on decreased fibrinogen recovery 2 g every 2 weeks	> 50 mg dL^{-1} for 26 days	Decrease in intracranial hematoma Right femoral line placed Persistent hemiparesis	DVT in inferior vena cava (catheter-related) and PE at day 72
Mehart, 1998 [40]	Afib undetectable Ag	Right parietal and occipital hematoma Right cerebellar hemorrhage Edema at 1 week	M	30 years	FC FC FC: prophy	10 g every 5 days for 40 days (first episode) 4.5 g 3× per week (second episode 18 months later) 3 g 2× per week for 1 month	≥ 150 mg dL^{-1}	Resorption of intracerebral hematomata at 1 month Resorption of hematoma Dysarthria and edema	None
Garcia-Monco, 1996 [41]	Afib	Bilateral vertebral artery dissection with ischemic infarct; evidence of old CNS hemorrhage	F	28 years	Cryo UHF, ticlopidine UFH Warfarin FC	NA 10 days, ticlopidine; day 11 on Recurrence a few days later; 10 days 3 months 3 months	≥ 100 mg dL^{-1}	Mild residual right upper arm incoordination	None

Table 2 Continued

Author, year, reference	CFD type	Treatment indication	Sex	Age	Fibrinogen source and relevant concomitant medications	Dose/dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Henselmans, 1999 [10]	Afib	Right hemiparesis; (hemorrhage negative on MRI) Recurrent right hemiparesis PE on day 21 following recurrent hemiparesis Recurrent headache, hemiparesis, dysarthria Recurrent PE	F	22 years	Cryo: Resume Cryo LMWH day 21 twice daily for 3 months for PE Resume LMWH FC	20 g per weekfor 2.5 weeks, off 2 weeks 18 g per weekfor 2 weeks 10 g per week for 3 months 5 g per week for 2 weeks 2.5 g per week for 2 weeks 20 g over 3 days 5 g per week for 2 weeks 20 g per week for 2 weeks Switch to FC 4.5 –3.5 g 2× per week	75 mg dL^{-1} (trough)	FC with lovenox effective and safe	Recurrent neurologic signs on Cryo 5 g once weekly PE Recurrent PE Poor plasma recovery of fibrinogen without evidence of antibodies on Cryo Possibility that episodes were primarily thrombotic
Vakalopoulou, 2006 [11]	Afib Ag 2 mg dL^{-1}	Intramuscular hematoma, thigh	M	22 years	FC 9 U packed red cells FC 5 U packed red cells FC	First hospitalization 75 mg kg^{-1} over 3 days 50 mg kg^{-1} every 12–17 h for 3 days, for a total of 12 g 25 mg kg^{-1} Second hospitalization Recurrence at 2 months 50 mg kg^{-1} over 24 h 12.5 mg kg^{-1} every 12 h for 4 days	Hemorrhage progressed with 50 mg dL^{-1} Bleeding controlled with > 75 mg dL^{-1} 60–80 mg dL^{-1} 45–55 mg dL^{-1} > 75 mg dL^{-1}	Recurrent hematomata requiring four hospitalizations. Ultimate resolution	Anaphylaxis with fibrinogen concentrate during childhood Hypertension
Parameswaran, 2000 [7]	Afib 9 mg dL^{-1}	Left frontal and left occipital ICH	M	27 years	Cryo FC: bleeding FC: prophy	15 bags 2 g initially 50 mg kg^{-1} twice weekly	> 100 mg dL^{-1} > 50 mg dL^{-1}	Neurologic status improved	None

Table 2 Continued

Author, year, reference	CFD type	Treatment indication	Sex	Age	Fibrinogen source and relevant concomitant medications	Dose/dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Pediatric (4 weeks to < 18 years of age)									
De Vries, 1961 [12]	Afib	Endocarditis Left knee hemarthrosis	F	16 years	FC	First hospitalization 3 g initially 3 g at 3 weeks Second hospitalization at 47 days 3 g Third hospitalization at 57 days Intermittently for 4 months	120 mg dL^{-1} 130 mg dL^{-1} 125 mg dL^{-1}	Possible subacute bacterial endocarditis Pneumonia Bacterial endocarditis Bleeding temporarily controlled; Circulating anti-fibrinogen antibody detected at 4 months after nine FC exposures, death at 7 months	Anti-fibrinogen antibody associated with anaphylaxis and skin reaction Rheumatic valvular heart disease Pulmonary infarction with cardiac mural thrombi on autopsy
De Mattia, 1993 [15]	Afib 10 mg dL^{-1} PC deficiency 50 U dL^{-1} activity and antigen	Ischemic thrombosis of the right 2nd–4th toes following prolonged marching and FC infusion	F	13 years	FFP UFH Pentoxifylline, nifedipine, LMW dextran 40	10 mL kg^{-1} 4 U kg^{-1}	NA	Complete resolution of ischemic lesion in 3 months	FC infusion several days prior to ischemic episode
Korte, 1994 [16]	Afib	Fibrous dysplasia Menorrhagia	F	13 years	FC	4-g single infusion	90 mg dL^{-1}; plasma $t_{1/2}$ ~ 12 h	Increased F_{1+2} at presentation; decreased with fibrinogen replacement, and increased again when fibrinogen fell to very low levels; DD rose following FC and decreased over 48 h	None
Rodriguez, 1988 [42]	Afib	Hematoma	F	11 years	Cryo: prophy	75 mg kg^{-1} $week^{-1}$ age 12–24 months 58 mg kg^{-1} every 10 days age 2–3 years	135 mg dL^{-1}	Prevented serious hemorrhage	None
Ehmann, 1994 [43]	Afib 15 mg dL^{-1}	Spontaneous splenic rupture	M	10 years	Cryo	~ 115 mg kg^{-1} (17 U per 37 kg) 8 U PRC ~ 135 mg kg^{-1} (20 U daily over 17 days)	161 mg dL^{-1} 100–200 mg dL^{-1}	Recovered	None

Table 2 Continued

Author, year, reference	CFD type	Treatment indication	Sex	Age	Fibrinogen source and relevant concomitant medications	Dose/dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Angles-Cano, 2007 [44]	Afib < 2.3 mg dL^{-1}	Compressive rectosigmoidal obstruction by hematoma	F	9 years	FC	Every 48 h for 8 days	NA	Resolved	None
Mehta, 1989 [45]	Afib	Excessive and uncontrollable bleeding from erupted tooth	F	8 years	FC	500-mg single dose	NA	Bleeding ceased within hours	None
Ehmann, 1994 [43]	Afib < 15 mg dL^{-1}	Traumatic splenic rupture	M	7 years	Cryo	~ 26 mg kg^{-1} (4 U per 39 kg) 3 U PRC Cryo daily for 8 days	63 mg dL^{-1} > 100 mg dL^{-1} trough	Recovered	None
Rodriguez, 1988 [42]	Afib	Extensive bruising	F	1.5 years	Cryo: prophy	~ 55–70 mg kg^{-1} (3 U) every 7–10 days from 18 to 33 months	NA	Prevented serious hemorrhage	None
Klarmann, 2005 [8]	Afib	Cranial epidural bleeding	M	1 year	FC	NA 1 g every 5 days; ongoing	Trough ≥ 100 mg dL^{-1} for 2 months 45 mg dL^{-1} trough	No further bleeding events	None
Thompson, 1998 [46]	Afib	Prophylaxis	M	2 years	Cryo: prophy	~ 58 mg kg^{-1} ~ 112 mg kg^{-1} every 2 weeks	84 mg dL^{-1} 155 mg dL^{-1}	Minimal bleeding	None
Patiroglu, 2006 [13]	Hypofib	Posterior parietal subdural hematoma	F	13 years	FFP rFVIIa	NA 80 μg kg^{-1}	Days 1, 3, 5	Recovery	Right middle cerebral artery occlusion on day 6; relationship to FFP or rFVIIa unknown
Datta, 2006 [47]	Hypofib (44 mg dL^{-1})	Septic arthritis of the knee	F	10 months	Cryo	~ 52 mg kg^{-1} (2 U) initially ~ 26 mg kg^{-1} (1 U) every other day for four additional doses	100 mg dL^{-1}	Improvement	None

Table 2 Continued

Author, year, reference	CFD type	Treatment indication	Sex	Age	Fibrinogen source and relevant concomitant medications	Dose/dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Neonate (birth to < 4 weeks of age)									
Parameswaran, 2000 [7]	Afib	Intracranial hemorrhage Recurrent intracranial hemorrhage at 1 year	M	4 days	Cryo Cryo FC	~ 71 mg kg^{-1} (1 U) 3× per week for 3 months ~ 72 mg kg^{-1} (3 U) 230 mg^{-1} kg^{-1} $week^{-1}$ for 10 months Prophyaxis decreased	100 mg dL^{-1} trough 50 mg dL^{-1} trough	Hemiparesis, focal seizure, hydrocephalus Developmental delay but improving	None
Toledano, 2008 [6]	Afib	Injection site hematomas	M	2 days	FC	300 mg kg^{-1} 160 mg kg^{-1}	42 mg dL^{-1} at 33.5 h 100 mg dL^{-1} at 48 h trough	Resolved	Hypocalcemia (3.58 mg dL^{-1}) possibly related to citrate in FC

Afib, afibrinogenemia; Ag, antigen; CFD, congenital fibrinogen deficiency; CNS, central nervous system; Cryo, cryoprecipitate; DD, d-dimer; DVT, deep vein thrombosis; Dysfib, dysfibrinogenemia; F, female; FC, fibrinogen concentrate; FDP, fibrin degradation products; FFP, fresh frozen plasma; Hypofib, hypofibrinogenemia; ICH, intracranial hemorrhage; IV, intravenous; LMW, low molecular weight; LMWH, low molecular weight heparin; M, male; MRI, magnetic resonance imaging; NA, not available; IVC, inferior vena cava; OCP, oral contraceptive pills; PC, protein C; PE, pulmonary embolism; prophy, prophylactic fibrinogen replacement; PRC; rFVIIa, recombinant activated FVII; SC, subcutaneous; UFH, unfractionated heparin. Treatment is provided for bleeding unless otherwise indicated.

given 55–110 mg kg^{-1} every 1–2 weeks. Two adults with intracranial events complicated by pulmonary embolism (PE) were successfully treated with trough fibrinogen levels of 50 and 75 mg dL^{-1} in addition to anticoagulation [9,10]. Treatment duration ranged from a single infusion for an erupting tooth and menorrhagia to long-term prophylaxis. There was one report of failure to control bleeding in a 22-year-old male with thigh muscle bleeding, which progressed with FRT to 50 mg dL^{-1}, required four hospitalizations, and stabilized with FRT to > 75 mg dL^{-1} [11].

Adverse events

Inhibitory antibodies and allergic reactions Fibrinogen antibodies and anaphylaxis developed in a 16-year-old female with bacterial endocarditis and thrombosis concomitant with loss of efficacy of FRT [12]. A 22-year-old female manifested poor plasma fibrinogen recovery with no detectable antibody in the context of severe thrombosis [10]. In addition, one episode of anaphylaxis during childhood was described in a 22-year-old male, who continued to receive FC with no further reactions [11].

Thrombotic complications Two afibrogenemic patients developed thrombotic complications temporally associated with FRT. A 35-year-old female receiving FC for recurrent ICH developed a catheter-related femoral vein and inferior vena cava deep vein thrombosis (DVT) with PE [9]. A 13-year-old female with ICH developed a right middle cerebral artery occlusion 6 days after treatment with FFP and recombinant activated FVII, at 80 μg kg^{-1} [13].

In four cases, the relationship of vascular occlusion to FRT, as opposed to being spontaneous, could not be determined. It could be speculated that thrombin generated within a hematoma and unregulated by fibrin binding in the afibrinogenemic state could cause platelet and cellular activation resulting in vascular occlusive and embolic lesions, as suggested in four cases:

Case 1: A 36-year-old female received periodic FC infusions for menorrhagia and hemarthrosis [14] (Table 2). Approximately 7 months later, the patient suddenly and unexpectedly died, and autopsy disclosed a large intraparenchymal ICH, narrowing of the thoracic and abdominal aorta, diffuse arteriosclerosis, and occlusion of the left internal carotid, vertebral and subclavian arteries.*Case 2*: A 22-year-old female presented with acute-onset right hemiparesis but negative magnetic resonance imaging findings [10] (Table 2). She was treated intensively with Cryo for clinically suspected ICH. After development of recurrent PE while she was receiving Cryo, and in spite of focal neurologic abnormalities, she was treated with enoxaparin supported with FC; both neurologic and pulmonary abnormalities resolved following institution of anticoagulation therapy.*Case 3*: A 13-year-old girl with afibrinogenemia and protein C deficiency (30 U dL^{-1}) was treated with a single infusion of FC for trauma related to intensive marching [15] (Table 2). Several days later, she

presented with ischemic thromboses of the second to fourth toes of the right foot. She was treated with very low-dose unfractionated heparin (4 U kg^{-1}), a single infusion of FFP (10 mL kg^{-1}), pentoxifylline, and nifedipine, and experienced complete resolution of the ischemic lesions over 3 months. Although protein C deficiency could have precipitated the thromboses, it is also possible that afibrinogenemia contributed to excess thrombin generation.

Case 4: In this case of a teenager with afibrinogenemia presenting with hemarthrosis, bacterial endocarditis was found [12] (Table 2). It is possible that spontaneous valvular thrombosis preceded the presentation with fever and hemarthrosis, as she did not respond to intensive medical support and, on autopsy, was found to have extensive pulmonary infarction, cardiac mural thrombi, and cardiac valvular lesions. This patient developed an inhibitory antibody following nine exposures to fibrinogen, with failure to increase plasma fibrinogen concentration; under these circumstances, the extensive thrombosis was even more remarkable.

Evidence of excessive thrombin generation in the afibrinogenemic state was also suggested in a 13-year-old female who presented with menorrhagia [16]. An elevated level of prothrombin fragment F_{1+2} was detected in her plasma prior to replacement with FC; the level of F_{1+2} decreased following FC infusion, and rose again when the fibrinogen plasma concentration decreased.

The difficulty in determining the cause of thrombosis is demonstrated by a case (not fulfilling eligibility for table inclusion) of a 16-year-old girl with afibrinogenemia who presented with chronic hepatic venous thrombosis (Budd–Chiari syndrome). Seven years previously, she had been diagnosed with ICH, and she underwent surgery followed by FRT until 2 years before presentation. Evaluation revealed no prothrombotic risk factors. Paradoxically, afibrinogenemia may be a risk factor for spontaneous vascular thrombotic events such as Budd–Chiari syndrome [17].

Other adverse events A 2-day-old infant developed hypocalcemia on receiving FC treatment for a hematoma [6]. This adverse event was judged to be possibly related to citrate present in the FC.

Pregnancy

Afibrinogenemia and pregnancy Seven women with afibrinogenemia received prophylactic FRT during 12 pregnancies. Five women had suffered a total of eight first-trimester abortions prior to using FRT preventively. However, even with fibrinogen prophylaxis, nine of 12 pregnancies had significant complications. One ectopic pregnancy was surgically removed at 9 weeks [18]. One pregnancy managed with FC at 15 g per week commencing at 10 weeks resulted in a stillborn infant at 24 weeks [19]. Where stated, target trough fibrinogen concentrations were above 60 mg dL^{-1} [20–22] or 100 mg dL^{-1} [19,22,23]. These target trough levels required 5–21 g per week of fibrinogen divided into two doses, and 15–30 g in three divided doses, respectively(Table 3).

Fibrinogen levels were 40, 25 and 0.9 mg dL^{-1} at the time of vaginal bleeding [23–25]. At the time of hemorrhage, however, it could not be determined whether the low fibrinogen concentration detected was the result of consumption with hemorrhage, shortened half-life, or inadequate replacement. Three pregnancies were terminated prematurely by placental abruption and retroplacental hematoma despite FRT to a monitored target of 60 or 100 mg dL^{-1} [21–23]. All three women manifested low fibrinogen levels at the time of abruption (33, 0.9 and 51 mg dL^{-1}). In two cases in which a pregnancy managed with monitored fibrinogen prophylaxis ended unsatisfactorily, FRT was initiated preconceptually for the subsequent pregnancy, and a higher fibrinogen concentration was maintained (mean 175–200 mg dL^{-1}); both pregnancies resulted in live-born infants [19,22].

There were no thrombotic complications during pregnancy. In one afibrinogenemic woman, previous arterial occlusive disease of the toes, which remitted during pregnancy, recurred following postpartum cessation of FRT [20].

One woman received Cryo prophylaxis during two pregnancies [22]. At the second delivery, multiple placental infarcts were noted. The slightly premature infant suffered surfactant deficiency but recovered. The mother suffered DVT on postpartum day 7, including left gonadal and renal vein thrombosis and possible PE.

Hypofibrinogenemia and pregnancy One of three women with hypofibrinogenemia had a history of prior poor pregnancy outcome without FRT, similar to women with afibrinogenemia, despite a mild or negative prepregnancy bleeding history. Regardless of prior history, women with hypofibrinogenemia were at risk for postpartum hemorrhage. There were no reports of lack of hemostatic efficacy, thrombotic events or other adverse outcomes in hypofibrinogenemic women with FRT in the reference range.

Dysfibrinogenemia and pregnancy Table 3 summarizes 23 pregnancies in eight women with dysfibrinogenemia [26–28]. Some affected women had minimal or no bleeding symptoms outside of pregnancy and childbirth. Dysfibrinogenemia patients experienced recurrent spontaneous first-trimester abortions and placental abruptions, similar to afibrinogenemic women. Women with dysfibrinogenemia and a history of recurrent poor pregnancy outcome were treated with prophylactic FC replacement as soon as pregnancy was confirmed, using a target trough fibrinogen level of 100 mg dL^{-1} [26–28]. In spite of substitution therapy, two of nine pregnancies resulted in spontaneous first-trimester abortion, two women experienced vaginal and retrochorionic hemorrhage, and one infant was delivered at 29 weeks following premature labor. There were no reports of failure to achieve hemostasis with normalization of plasma fibrinogen concentration.

Table 3 Dosing of fibrinogen replacement around the time of pregnancy

Author, year, reference	CFD type	Treatment indication	Age (years)	Fibrinogen source and relevant concomitant medications	Dose/Dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Takahashi, 1995 [20]	Afib	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3	36	No replacement No replacement FC: prophy	Calculations based on prepregnancy weight 1–22 weeks: 80 mg kg^{-1} $week^{-1}$ (4 g) in two divided doses 23–28 weeks: 100 mg kg^{-1} $week^{-1}$ (5 g) 29–33 weeks: 140 mg kg^{-1} $week^{-1}$ (7 g) 34 weeks: 180 mg kg^{-1} $week^{-1}$ (9 g) 35 weeks: 220 mg kg^{-1} week (11 g) 36–37 weeks: 300 mg $^{-1}$ kg^{-1} $week^{-1}$ (15 g) 38 weeks: planned cesarean: 100 mg kg^{-1}, 60 mg kg^{-1} postoperatively 80 mg kg^{-1}day until 6th postpartum day	NA NA 70 mg dL^{-1} > 60 mg dL^{-1} > 60 mg dL^{-1} > 60 mg dL^{-1} > 60 mg dL^{-1} During C/S 190 mg dL^{-1}	Spontaneous abortion at 2–3 weeks Spontaneous abortion at 2–3 weeks Live-born delivery	Arterial ischemic occlusive disease in the left toes, which had been present prepregnancy, recurred following cessation of FC
Inamoto, 1985 [24]	Afib	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3	34	No replacement No replacement FC: bleeding and prophy	5 weeks: 3 g for vaginal bleed; then 8 g $week^{-1}$ 8 weeks: 2–4 g $week^{-1}$ 20 weeks: 12 g $week^{-1}$ for vaginal bleed, 20–37 weeks: 6 g $week^{-1}$ 37 weeks: 8 g at time of planned cesarean 6–12 g $week^{-1}$ for 2 weeks	NA NA NA 5–40 mg dL^{-1} trough 40 mg dL^{-1} at time of bleeding 84 mg dL^{-1} at cessation of bleeding 20–40 mg dL^{-1} trough 120 mg dL^{-1} 60–120 mg dL^{-1} trough	Spontaneous abortion Spontaneous abortion Live-born delivery	None

Table 3 Continued

Author, year, reference	CFD type	Treatment indication	Age (years)	Fibrinogen source and relevant concomitant medications	Dose/Dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Kobayashi, 1996, 2000 [21,25]	Afib	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3 Pregnancy no. 4	28	No replacement No replacement FC: vaginal bleeding and prophy FC: prophy	4 weeks: 4 g $week^{-1}$ 5–15 weeks: 7 g $week^{-1}$ divided into 2–4 doses 15–25 weeks: 10 g $week^{-1}$ divided into 2–4 doses 25–30 weeks: 14 g $week^{-1}$ divided into 2–4 doses 30–37 weeks: 10 g $week^{-1}$ divided into 2–4 doses 37 weeks: 10 g for emergent cesarean 1–5 days postpartum: 2 g per day 6–10 days postpartum: 1 g per day 5 weeks: 2 g × 2 for vaginal bleed 8 weeks, continued bleeding, 6 g 8 weeks to term: 12–21 g per week 36 weeks: 8 g during and after cesarean	≥ 60 mg dL^{-1} trough until delivery 33 mg dL^{-1} at abruption 147 mg dL^{-1} during cesarean 199 mg dL^{-1} following cesarean 25 mg dL^{-1} 139 mg dL^{-1} at cessation of bleeding > 200 mg dL^{-1} during cesarean	Spontaneous abortion Spontaneous abortion Abruptio placenta Live-born delivery Live-born delivery	None None
Grech, 1991 [19]	Afib	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3	30	Cryo: bleeding FC: prophy FC: prophy	NA 10–24 weeks: 15 g $week^{-1}$ Started pre-conception: 100 mg kg^{-1} 3× weekly 24 weeks: 170 mg kg^{-1} 3×	NA 100 mg dL^{-1} 170–220 mg dL^{-1}	Spontaneous abortion 7 weeks Stillborn 24 weeks Live-born delivery	None
Matsushita, 2008 [18]	Afib	Pregnancy no. 1	25	FC: prophy	6–9 weeks: 2–3 g every 2–3 days	80–158 mg dL^{-1} during pregnancy; 76–139 mg dL^{-1} postoperatively	Ruptured ectopic pregnancy 9 weeks	None

Table 3 Continued

Author, year, reference	CFD type	Treatment indication	Age (years)	Fibrinogen source and relevant concomitant medications	Dose/Dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Trehan, 1991 [23]	Afib	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3	25	No replacement FC: prophy FC: prophy	NA 5–13 weeks: multiple episodes of vaginal bleeding with intermittent FC infusions 13–27 weeks: 5 g weekly 0–7 weeks: 5 g every 8–10 days 7–39 weeks: 7–10 g, 3× per week Induction of labor: 10 g Postpartum: 5 g 3× per week for 4 weeks	NA ≥ 100 mg dL^{-1} 0.9 mg dL^{-1} at abruption ≥ 100 mg dL^{-1} ≥ 150 mg dL^{-1} during delivery	Spontaneous abortion 7 weeks with bleeding 27 weeks abruptio placenta, 610-g infant died Live-born delivery	None None
Roqué, 2004 [22]	Afib	Pregnancy no. 1 Pregnancy no. 2	NA	Cryo: prophy Cryo: prophy	2–36 weeks: 20–25 U (∼ 5–6.25 g) 2× per week Pre-conception to 34.5 weeks: 20–25 U (∼ 5–6.25 g) 2× per week	60 mg dL^{-1} 205 mg dL^{-1} within 24 h of abruption and 51 mg dL^{-1} at time of abruption Mean 175 mg dL^{-1} (range 108–235) Trough mean 81 mg dL^{-1} (range 17–112)	Abruption at 35.6 weeks; emergency cesarean; wound dehiscence; infant survived and recovered Cesarean live-born at 34.5 weeks; required surfactant therapy; maternal wound dehiscence	Placental abruption and retroplacental hematoma Placental infarcts Maternal left gonadal vein thrombosis, left renal vein thrombosis day 7 postpartum; possible PE
Goodwin, 1989 [48]	Hypofib (80–90 mg dL^{-1})	Pregnancy no. 1	31	Cryo: bleeding	33 weeks: 14 U before emergent cesarean delivery for recurrent vaginal hemorrhage and placental abruption	112 mg dL^{-1} in recovery room	Live-born delivery	None
McLeod, 1989 [49]	Hypofib (66 mg dL^{-1} Act; 38 mg dL^{-1} Ag)	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3	27	PRBC postpartum FFP: prophy for delivery Cryo: prophy for delivery	NA NA 4.45 g × 3 over 12 h	Postpartum extensive vaginal and uterine hemorrhage Less severe hemorrhage 125 mg dL^{-1} preinfusion); (> 200 mg dL^{-1} postpartum	Live-born infant	None None

Table 3 Continued

Author, year, reference	CFD type	Treatment indication	Age (years)	Fibrinogen source and relevant concomitant medications	Dose/Dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Kitchens, 1987 [50]	Hypofib	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3 Pregnancy no. 4	25	No replacement No replacement Cryo: prophy Declined replacement	NA NA 5 weeks vaginal bleeding: 10 U (2.5 g) to stop spotting 5–12 weeks: 10 U (2.5 g) per week 12 weeks to term – 4–9 weeks postpartum: vaginal hemorrhage	NA NA 50 mg dL^{-1} with bleeding 150 mg dL^{-1} mean; range 105–275 mg dL^{-1} 200 mg dL^{-1} without replacement	Spontaneous abortion 11 weeks Spontaneous abortion 7 weeks Live-born delivery Spontaneous abortion 9 weeks	None
Miesbach, 2009 [26]	Dysfib	Four pregnancies	30.5 median $N = 4$	FC: prophy LMWH 40–60 mg day^{-1} SC postpartumfor 14 days	Four cases: two homozygotes, 10, 20 mg dL^{-1} fibrinogen activity; two heterozygotes 38, 51 mg dL^{-1} fibrinogen activity 3, 2, 1, 1 weeks preceding spontaneous abortions in four patients at 2–10 weeks 3, 4, 6, 6 weeks to end of pregnancy: 2–3 g 2× or 3× per week	> 100 mg dL^{-1} 82–176 mg dL^{-1}	Three of four pregnancies successful; one, who began replacement therapy at 6 weeks of gestation, miscarried at 9 weeks	None
Yamanaka, 2003 [27]	Dysfib	Pregnancy no. 1 Pregnancy no. 2 Pregnancy no. 3 Pregnancy no. 4 Pregnancy no. 5	38	No replacement No replacement No replacement No replacement FC: prophy	8 weeks: 2 g 3× per week 16 weeks: 10–14 g per week for vaginal bleeding and uterine contractions 29 weeks: emergent cesarean for premature labor, 6 g fibrinogen by continuous infusion before and during cesarean; continued replacement (unspecified) for 7 days postpartum	NA NA NA NA > 100 mg dL^{-1} 138 mg dL^{-1} at time of vaginal bleeding 191 mg dL^{-1} at time of premature labor	Spontaneous abortion 8 weeks Spontaneous abortion 8 weeks Placental abruption 25 weeks Placental abruption 26 weeks Dysfibn diagnosis Cesarean live-born at 29 weeks	None

Table 3 Continued

Author, year, reference	CFD type	Treatment indication	Age (years)	Fibrinogen source and relevant concomitant medications	Dose/Dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Aygören-Pürsün, 2008 [28]	Dysfib	Pregnancy no. 1	23	No replacement		NA	Spontaneous abortion	None
		Pregnancy no. 2	Sister	No replacement		NA	6 weeks	None
		Pregnancy no. 3		No replacement		NA	Spontaneous abortion	
		Pregnancy no. 4		FC: prophy		49–83 mg dL^{-1}	11 weeks	
		Pregnancy no. 1		FC: prophy		48 mg dL^{-1} median, interquartile range 45–66	Spontaneous abortion 7 weeks	
						44 mg dL^{-1} median, interquartile range 40–44	Cesarean live-born delivery at week 38	
						70–90 mg dL^{-1}	Retrochorionic hematoma at 7th week; resolved over 6 weeks	
							Cesarean live-born	

Act, activity; Afib, afibrinogenemia; Ag, antigen; CFD, congenital fibrinogen deficiency; C/S, Cesarean section delivery; Cryo, cryoprecipitate; Dysfib, dysfibrinogenemia; FC, fibrinogen concentrate; FFP, fresh frozen plasma; Hypofib, hypofibrinogenemia; LMWH, low molecular weight heparin; NA, not available; PE, pulmonary embolism; PRBC, packed red blood cells; prophy, prophylaxis; SC, subcutaneous.

Surgery

Hemostatic efficacy Plasma fibrinogen activity levels achieved around the time of surgery generally ranged between 100 and 200 mg dL^{-1} [29–37]. There were two cases of potential lack of hemostatic efficacy associated with the use of FRT for prophylaxis of surgical bleeding. An intracranial hematoma recurred and expanded 12 h following surgical evacuation [29]. The patient received 3 g of FC preoperatively, and achieved a plasma fibrinogen activity of > 100 mg dL^{-1}. A second evacuation was immediately performed with adequate hemostasis. A child developed oozing at the site of surgical splenectomy on postoperative day 22, 5 days following his last infusion of FC [35]. Anaphylaxis developed that was temporally related to the FRT given for the oozing (Table 4).

Thrombotic complications around the time of surgery Thrombosis complicated the perioperative course of five of five adults with afibrinogenemia and of a young adult with dysfibrinogenemia. Thrombotic episodes included bypass reocclusion during prophylaxis with low molecular weight heparin and aspirin, and progressive mesenteric venous thrombosis necessitating two operations [31,32]. There were three cases of postoperative PE and one of DVT [29,30,33,37]. Three of the six postsurgical thromboses occurred in patients who had additional thrombotic episodes that were not temporally related to FRT [31,37]. The patient with bypass reocclusion initially presented with severe stenosis of the right iliac artery, occlusion of the hypogastric artery and multiple occlusive emboli to the toes in the absence of FRT [31]. Histologic examination of the vascular lesions revealed severe medial hyperplasia originating within a vascular hematoma. It was hypothesized that local generation of excess thrombin within the arterial wall, unregulated by fibrin binding in the afibrinogenemic state, stimulated severe medial cellular proliferation. Histologic evidence for inflammation and atherosclerosis was lacking. One patient with dysfibrinogenemia had suffered previous lower extremity DVT and thrombophlebitis not associated with FRT, and, following a hysterectomy at age 22 years, developed a PE [37]. Her affected father died at age 41 years with spontaneous PE.

Although no child suffered clinical thrombosis, a 13-year-old undergoing repair of a calcified bicuspid aortic valve had an excessively short reaction time on thromboelastogram (4.3 min, reference range 10–14 min) while on Cryo replacement, despite prophylaxis with unfractionated heparin.

Discussion

There are no formal US guidelines on the use of FRT in the treatment of CFD. The UK Haemophilia Centre Doctors published treatment guidelines for afibrinogenemia in 2004, based on expert opinion [38]. Their recommendations for FRT to 100 mg dL^{-1} for hemostasis and to 50 mg dL^{-1} for wound healing are similar to this reported patient experience, but dose,

Table 4 Dosing of fibrinogen replacement to prevent surgical bleeding

Author, year, reference	CFD type	Procedure	Sex	Age (years)	Fibrinogen source and relevant concomitant medications	Dose/Dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Adult (≥ 18 years of age)									
Pati, 2009 [29]	Afib	Craniotomy, drainage of epidural and subdural hematomas	F	32	FC	3 g at first surgery 2 g every other day after second surgery	> 100 mg dL^{-1} 50–100 mg dL^{-1}	Intracranial hematomas recurred, requiring second evacuation	PE+ during third week postoperatively
Haberer, 2008 [30]	Afib	Eye enucleation	F	30	FC	4.5 g preoperatively 1.5 g days 1 and 2 postoperatively	≥ 100 mg dL^{-1}	Uneventful	3 cm left calf DVT postoperative day 4; no treatment, no progression
Dupuy, 2001 [31]	Afib	Arteriography and surgical bypass for severe stenosis of the right iliac artery and occlusion of the hypogastric artery with necrotic embolic lesions to the 3rd–5th toes	M	30	FC	3 weeks (dosing NA) Lovenox 40 mg day^{-1} started immediately postoperatively ASA 100 mg started postoperative day 3	≤ 130 mg dL^{-1}	Reocclusion following surgery; recurrence in the left iliac artery 3 years later	Bypass occlusion by thrombus on day 3 despite fibrinogen replacement, lovenox and ASA
Takasugi, 2005 [32]	Afib	Mandibular abscess Peritonitis, small bowel resection Resection of adhesions	M	19	FC FFP FFP FC	9 g 10 U (2.5 g) 8 U (2 g) 5 g	191 mg dL^{-1} 226 mg dL^{-1} 103 mg dL^{-1}	Uneventful Found thrombosed bowel, resected all but 60 cm Recovered	Further thrombosis at 24 h Increased TAT, D-dimer, decreased platelets preoperatively
Cronin, 1988 [33]	Afib	Right subtalar and left ankle joint arthrodesis for posthemorrhagic arthropathy	F	24	Cryo OCPs Tranexemic acid	Preoperatively and postoperatively	100–180 mg dL^{-1} FVIII 255 IU dL^{-1} at time of PE	NA	Day 15 postoperatively, multiple segmental and subsegmental PE
Hattersley, 1969 [34]	Hypofib (119 mg dL^{-1})	Hysterectomy (huge uterine mass obstructing the bladder possibly related to recurrent hemorrhages associated with childbirth ×4)	F	50	Cryo	25 mg kg^{-1} 1 day prior to surgery 25 mg kg^{-1} just prior to surgery 25 mg kg^{-1} day 2 postoperatively	200 mg dL^{-1} 325 mg dL^{-1} 225 mg dL^{-1}	Uneventful hysterectomy	None

Table 4 Continued

Author, year, reference	CFD type	Procedure	Sex	Age (years)	Fibrinogen source and relevant concomitant medications	Dose/Dose frequency	Fibrinogen level achieved	Outcome	Adverse events
Pediatric (4 weeks to < 18 years of age)									
Shima, 1997 [35]	Afib	Splenic rupture (splenectomy)	M	14	FFP FC	21 mg kg^{-1} fibrinogen 200 mg kg^{-1} around the time of surgery 111 mg kg^{-1} postoperative days 1 and 2 89 mg kg^{-1} postoperative days 3–7 67 mg kg^{-1} postoperative days 8–11	210 mg dL^{-1} > 100 mg dL^{-1} for 10 days postoperatively	Satisfactory hemostasis	None
Lal, 2005 [36]	Afib	Aortic valve repair (calcified bicuspid valve), mean gradient 60 mm, area 0.3 cm^2	M	13	Cryo Aprotinin: 1×10^6 U; 1 U kg^{-1} h^{-1} Unfractionated heparin 312 U kg^{-1}	Following protamine 15 mg, Cryo ~ 5 g (20 U) during CPB 10 U at 48 h	124 mg dL^{-1} 42 mg dL^{-1} trough 102 mg dL^{-1}	Resolved	None clinically Very short reaction time on TEG following Cryo (reaction time = 4.3 min, with normal range 10–14)
Shima, 1997 [35]	Afib	Splenic rupture (failed splenic suturing and subsequent splenectomy)	M	11	FFP FC	30 mg kg^{-1} 93 mg kg^{-1} preoperatively 116 mg kg^{-1} postoperatively days 1, 2, 3 93 mg kg^{-1} postoperative days 4, 5, 6 93 mg kg^{-1} day 17 postoperatively at time of suture removal	110 mg dL^{-1} 180 mg dL^{-1} 120 mg dL^{-1} trough day 3	Oozing at wound site day 22 postoperatively	Anaphylactic reaction (sudden dyspnea and hypotension) after infusion 22 days postoperatively
Franz, 2002 [37]	Dysfib (70 mg dL^{-1})	Spontaneous intracranial hemorrhage Resection of colonic stricture secondary to ulcerative colitis Hysterectomy	F	12 17 22	None specified FFP Cryo	2 U NA	NA NA	Minimal bleeding No hemorrhage	LLE DVT and RLE thrombophlebitis not associated with replacement therapy Postoperative PE Affected father died at age 41 years with spontaneous PE

Afib, afibrinogenemia; ASA, aspirin; CFD, congenital fibrinogen deficiency; CPB, cardiopulmonary bypass; Cryo, cryoprecipitate; DVT, deep vein thrombosis; Dysfib, dysfibrinogenemia; F, female; FC, fibrinogen concentrate; FFP, fresh frozen plasma; Hypofib, hypofibrinogenemia; LLE, left lower extremity; M, male; NA, not available; OCP, oral contraceptive pills; PE, pulmonary embolism; RLE, right lower extremity; TAT, thrombin-antithrombin complexes; TEG, thromboelastogram.

dose frequency and duration of therapy were not addressed. Although the UK report acknowledged an association of thrombosis in patients with dysfibrinogenemia, as well as in 4% of patients with afibrinogenemia, it did not address thrombotic effects of FRT. In addition, although the UK physicians noted the high rate of pregnancy complications, and suggested the importance of fibrinogen in implantation, they did not offer any specific recommendation with regard to management of pregnancy in women with CFD. A UK Physicians update in 2008 listed FC as the replacement product of choice for CFD, but did not address dosing, efficacy or adverse events of FRT [39].

With an estimated prevalence of afibrinogenemia at one per 10^6 live births, there should be 300 US patients. However, a systematic review of the English language medical literature provided only 50 cases in which sufficient data regarding fibrinogen dosing and outcome were provided to inform a treating physician. The current literature review is consistent with the recently published pharmacokinetic study of an FC, in which it was possible to enroll only 15 afibrinogenemic subjects [4]. It is probable that CFD severe enough to come to medical attention and require the service of specialized coagulation programs is very rare.

The small patient number notwithstanding, the current review provides valuable information with which to guide FRT in various clinical circumstances. In the reports reviewed, FRT for most severe bleeding events, such as ICH, was dosed initially to maintain the plasma fibrinogen concentration above 100 mg dL^{-1}. Most cases of inadequate hemostatic control or early recurrence were associated with fibrinogen levels below 75 mg dL^{-1} at the time of hemorrhage. The determination of an antibody directed against infused fibrinogen was a very rare event, the presence of the antibody being proven in one of the 50 patients, and suspected, but not proven, in a second. However, plasma clearance of fibrinogen was often accelerated in the setting of acute bleeding, and dose frequencies based on monitored levels resulted in dosing every 2–5 days during the acute course, followed by dosing every 1–2 weeks during the subacute to chronic phase of healing. Another indicator of accelerated fibrinogen consumption during acute hemorrhage was noted in the initial dosing. Adult patients were initially dosed with 8–10 g of fibrinogen replacement to achieve the targeted level, and maintained on doses of 2–4 g.

Data on 18 obstetric patients confirmed the very high rate of spontaneous first-trimester abortion in women with afibrinogenemia. Even when FRT was begun by 5 weeks of gestation, vaginal and retrochorionic bleeding were common. In cases where early substitution therapy failed, FRT initiated prior to conception with higher target levels resulted in successful live deliveries. Placental abruption is a particularly vexing complication of afibrinogenemia, and was not completely prevented by FRT. Fibrinogen activity was usually below the target level at the time of abruption, but it was not possible to reconstruct whether the low level developed from hemorrhagic consumption or preceded placental abruption. Fibrinogen clearance increased markedly as pregnancy advanced, requiring higher and more frequent dosing to maintain a target trough of 100 mg dL^{-1}. Prophylactic FRT during pregnancy ranged from 2 g twice weekly during the first trimester to 5 g three to four times per week at term. The reported pregnancies in patients with dysfibrinogenemia were very similar in complications and outcome to pregnancies in those with afibrinogenemia. In contrast, only one of three pregnancies in patients with hypofibrinogenemia resulted in recurrent abortion prior to successful pregnancy with fibrinogen prophylaxis. All three hypofibrinogenemic women had no bleeding symptoms prior to childbirth, and responded to FRT for the delivery and postpartum period. Thrombotic complications were rare in the obstetric population with CFD. In fact, one woman who had previous arterial ischemic occlusive lesions of her toes unrelated to FRT experienced no symptoms of this complication during pregnancy, but suffered recurrence postpartum following cessation of prophylactic FC.

Surgical procedures were generally performed with a fibrinogen level of 100–200 mg dL^{-1} following 50–100 mg kg^{-1} of fibrinogen in adults, and up to 200 mg kg^{-1} in children. Hemostasis was generally satisfactory. Perioperative thrombotic complications were particularly high around the time of surgery.

There is an established relationship between certain forms of dysfibrinogenemia and thrombosis [1,2]. Prothrombotic fibrinogen mutations have been identified that promote thrombosis through a variety of mechanisms, including decreased thrombin binding to defective fibrin, defective fibrin polymerization, defective assembly of the fibrinolytic system, or defective fibrinolysis, among others. However, the relationship between afibrinogenemia and thrombosis has been debated and poorly documented in the literature. The current review presents data that suggest a striking relationship between afibrinogenemia and thrombosis, especially in females and following puberty. Thrombotic complications were reported in afibrinogenemic patients, including five of 10 (50%) adults and teenagers with bleeding, and six of six (100%) adults undergoing surgery. In contrast, the rate of thrombosis in infants, children and pregnant women was very low. Furthermore, seven of 35 (20%) afibrinogenemic patients had a history of possible or definite thromboses that were not temporally related to FRT. Finally, laboratory evidence of increased coagulability was suggested in four patients. In some cases (Table 2, case 2 [9]; Table 4; case 3 [31]), patients with a longstanding history of afibrinogenemia and FRT over a number of years were found to have extensive, thrombotic vascular disease. In these cases, the likelihood of vascular disease being a consequence of afibinogenemia, as opposed to being caused by replacement therapy, cannot be determined. These cases were included because clinicians dealing with thrombotic complications in patients with afibrinogenemia are likely to encounter similarly complicated courses.

This study is limited by the very small number of published reports describing the use and outcome of FRT in patients with CFD. As such, the reports could be skewed towards either superior or less desirable outcomes. In addition, the extraction

and aggregation of data from individual case reports required an arrangement of histories to accommodate some comparison of dose, frequency, duration, and outcome. Despite these potential sources of error, the rather consistent dosing information regarding dose per kilogram, dose frequency and achieved trough level adds some strength to the findings for the clinician who seeks guidance regarding initial dosing for fibrinogen replacement. Obviously, there is no substitute for monitoring of fibrinogen activity after initiation of replacement therapy.

Conclusion

FRT is generally effective in the treatment or prevention of bleeding, including surgical bleeding, and in reducing the high rate of pregnancy loss. FC has enhanced theoretical viral safety and does not contain unnecessary prothrombotic coagulation proteins. The review disclosed a high rate of thrombosis in patients with congenital afibrinogenemia, both temporally related and distant to fibrinogen replacement therapy, particularly following surgery. The authors offer an expert consensus suggestion that patients with CFD be monitored carefully for laboratory and clinical evidence of coagulation activation and clot formation, and that careful consideration should be given to the use of prophylactic anticoagulation around the time of surgery and intensive FRT. In addition, a high rate of obstetric complications was determined that was reduced, but not eliminated, by prophylactic FRT initiated very early following conception. Prospective studies are needed to determine plasma fibrinogen threshold levels associated with adequate hemostasis and minimal thrombosis.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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