

Women With Congenital Hypofibrinogenemia/Afibrinogenemia: From Birth to Death

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Abstract

Congenital fibrinogen disorders are a group of most frequent rare coagulation disorder, characterized by deficiency and/or defects in the fibrinogen molecule. Quantitative disorders include hypofibrinogenemia and afibrinogenemia. Due to their specific physiological characteristics, female patients tend to have congenital hypofibrinogenemia/afibrinogenemia, such as spontaneous recurrent abortion, menorrhagia, infertility, antepartum and postpartum hemorrhage, and so on. Current studies of congenital hypofibrinogenemia/afibrinogenemia mainly focus on different types of fibrinogen mutations, etiology/pathogenesis, and some rare case reports of the diseases. So far, there is no study available to systematically review the specific features of female patients with congenital bleeding disorders. This review aims to deal with hematological, gynecologic and obstetric issues, and relevant clinical management of congenital hypofibrinogenemia/afibrinogenemia at different life stages of female patients. We believe this review provides valuable reference for clinicians in the field of hematology, obstetrics, as well as gynecology.

Keywords

congenital coagulation disorder, fibrinogen, hypofibrinogenemia, afibrinogenemia, women's health

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Introduction

Fibrinogen (FIB) is a plasma glycoprotein, synthesized in the liver and involved in the final step of the coagulation cascade, which plays a central role in the hemostatic process. Congenital FIB disorders are a group of most frequent rare coagulation disorder, characterized by deficiency and/or defects in the FIB molecule, the blood coagulation factor I.^{1,2} Diagnosis is established by demonstrating decreased activity and/or decreased levels of immunoreactive FIB in the plasma. Quantitative disorders include hypofibrinogenemia and afibrinogenemia, referring to decreased or absence of FIB, respectively. Qualitative disorders indicate normal or decreased levels of a dysfunctional FIB.² Congenital hypofibrinogenemia/afibrinogenemia is inherited as an autosomal recessive disorder. Proportional low values of functional and antigenic FIB levels may lead to various bleeding symptoms, ranging from mild bleeding, posttraumatic bleeding, and even life-threatening spontaneous bleeding.³ Paradoxically, thrombosis in both venous and arterial sites are also a typical complication of congenital FIB disorders, in addition to bleeding symptoms.^{4,5} In their study, the authors identified 2 novel FIB mutations in 2 Slovak families with quantitative FIB disorders and concluded the development

of thrombotic complications was spontaneous since the patient and his son did not receive substitution therapy with the FIB concentrate in the period of their recurrent thromboses manifestation.⁵

Due to their specific physiological characteristics, female patients tend to have congenital hypofibrinogenemia/afibrinogenemia, such as spontaneous recurrent abortion, menorrhagia, infertility, antepartum and postpartum hemorrhage, and so on.^{6,7} Current studies of congenital hypofibrinogenemia/afibrinogenemia mainly focus on different types of FIB mutations, etiology/pathogenesis, some rare case reports of the diseases,

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and the relationship of hotspot FIB gene mutations associated with recurrent deep vein thromboses as serious manifestation of thrombotic phenotype.⁸⁻¹² So far, there is no study available to systematically review the specific features of female patients with congenital bleeding disorders. This review aims to deal with gynecologic and obstetric issues and relevant clinical management of congenital hypofibrinogenemia/afibrinogenemia at different life stages of female patients.

Infancy and Childhood Manifestations and Clinical Management

Early onset of clinical manifestations often appears in severe cases, mostly patients with afibrinogenemia. Umbilical cord hemorrhage (unusual in hemophilia) or prolonged bleeding from umbilical stump is often the first bleeding episode in patients with congenital afibrinogenemia and also a common cause of neonatal mortality in this patient population. Intracranial hemorrhage (ICH) is also a common site of bleeding children with afibrinogenemia. Patiroglu and colleagues evaluated 107 children with congenital factor deficiencies (including hemophilia, FIB deficiency, and factor V/X/XIII/VII/XI deficiencies) in Turkey, among which 18 patients were observed to have ICH.¹³ Moreover, 6 (33.3%) patients with ICH had afibrinogenemia (plasma FIB level <100 mg/dL), far more than patients with ICH having other types of factor deficiencies. As for the reason why the risk of ICH was found to be higher in children with congenital hypofibrinogenemia/afibrinogenemia compared to other congenital factor deficiencies, the authors analyzed that congenital hypofibrinogenemia/afibrinogenemia is autosomal recessive. As the rate of consanguineous marriages in Turkey is high up to 21%, autosomal recessive disorders are seen at a higher than expected frequency in this population. Spontaneous hemarthrosis (knee and ankle hemarthroses) is another common symptom of congenital FIB disorders. In a recent paper, the authors described a typical case of afibrinogenemia having recurrent microbleeds to hip joint in childhood and requiring repeated total hip arthroplasty (at the age of 15 and 26 years, respectively).¹⁴ Less frequent manifestations in infancy and childhood include muscular hematomas, mucosal bleeding, and so on.¹⁵ A rare case was reported to bleed in the heel stick for 6 days in the newborn period, who was later diagnosed as congenital afibrinogenemia with undetectable FIB.¹⁶ A large Iranian cohort depicted clinical bleeding episodes in early age, including splenic rupture, a hemorrhagic corpus luteum at menarche, urinary tract, and central nervous system bleeding.¹⁷ Oral contraceptive medication prophylaxis is often placed to prevent ovulation-associated bleeding. As for the treatment before menarche, general management includes iron supplementations, local hemostatic measures, and lifestyle recommendations such as the avoidance of high bleeding risk activities, selection of invasive interventions with minimal bleeding risk recommended by specialists from the comprehensive center of hemostasis, and so on.¹⁸ For those with severe bleeding episodes, replacement therapy is still the best and sometimes only choice. Fibrinogen replacement

products include fresh frozen plasma (FFP), cryoprecipitates, and plasma-derived FIB concentrates. Among the above 3 products, plasma-derived FIB concentrates are recognized as the best choice, since it is safer than the other 2 counterparts in consideration of avoiding the risk of viral infection and fluid overload.¹⁹ Noticeably, it should be emphasized that FFP or cryoprecipitate can be used only in absence or unavailability of FIB concentrate. The whole blood transfusion should not be used at all, especially in young women to avoid potential allergy. A recently published review gave a systematic introduction of the pharmacological, clinical aspects and future perspectives on the utilization of FIB concentrates in the treatment and prevention of bleeding in patients with hereditary FIB disorders.²⁰

Menorrhagia: Most Common Symptom

Menorrhagia, defined as prolonged (lasting more than 7 days) or excessive uterine bleeding occurring at regular intervals, is a common problem in perplexing women of reproductive age.^{21,22} It is reported that approximately 30% (21) of reproductive women complain of heavy menses. Underlying bleeding disorders frequently appears among women with menorrhagia.²³⁻²⁵ Menorrhagia is considered as the most common, sometimes even the only symptom for patients with congenital hypofibrinogenemia/afibrinogenemia.^{6,7,26} Due to different defect levels of FIB, manifestations differ from asymptomatic, mild to severe menorrhagia; significant bleeding symptoms with surgery, trauma, and pregnancy; even recurrent postpartum hemorrhage; and so on.²⁶ The major therapeutic products used include FFP, cryoprecipitate, whole blood, and antifibrinolytics.²⁷ The levonorgestrel-releasing intrauterine system (LNG-IUS) has also been employed in the treatment of heavy menstrual bleeding. In a prospective single-center study in Turkey, the LNG-IUS was inserted in 60 patients diagnosed with heavy menstrual bleeding. After a 12-month observation, the researchers found that LNG-IUS insertion dramatically decreased visual bleeding scores. Confusingly, results from the same study also showed a significant reduction in the amount of FIB after LNG-IUS use.²⁸ But both the original and terminal levels of FIB were within normal range. A former trial displayed similar results, indicating a positive correlation between duration of bleeding and FIB degradation products for LNG-IUS users with idiopathic menorrhagia.²⁹ In contrast, combined oral contraceptive pill (COCP) usage led to decreased FIB levels,³⁰ indicating different effects and functioning mechanisms between estrogen and progesterone on hemostatic variables. Back to the case in our hospital (see the "Ruptured corpus luteum cyst" part for detail), although Mirena showed a satisfactory treating effect on patient with menorrhagia secondary to congenital hypofibrinogenemia, long-term follow-up is yet in need to testify the change in FIB levels during Mirena usage. Also, further studies should be launched to explore the underlying interaction between menorrhagia and coagulation disorders.

Ruptured Corpus Luteum Cyst

Although hypofibrinogenemia/afibrinogenemia theoretically increases the incidence of ruptured corpus luteum cyst and secondary intra-abdominal hemorrhage in luteal phase, intra-abdominal bleeding due to ovulation is very rare in these patients, and only a few cases of corpus luteum rupture and hemoperitoneum in patients with hypofibrinogenemia/afibrinogenemia have been reported. Kim and colleagues reported a case of an 18-year-old female patient with congenital hypofibrinogenemia who developed intra-abdominal hemorrhage due to a ruptured corpus luteum cyst.³¹ The woman was referred to with severe abdominal pain and dizziness. She was diagnosed with congenital hypofibrinogenemia in childhood, and her mother and grandmother had been diagnosed as congenital hypofibrinogenemia. Transvaginal ultrasonography suggested massive hemoperitoneum and a $6 \times 4 \times 4$ cm³ complex mass in right adnexal region. On admission, blood test indicated a plasma FIB level of 15 mg/dL (normal range: 160-350 mg/dL). Two hours after admission, the hemoglobin (Hb) dropped from 103 g/L to 74 g/L. Red blood cell suspension and FFP were transfused immediately. An emergency exploratory laparoscopy was performed, finding a ruptured ovulatory follicle on the right ovary. Approximately 2.5 L of blood was evacuated intraoperatively. The postoperative period was uneventful and prolonged low-dose oral contraceptive pills were prescribed. Unfortunately, the authors in the case report did not explain why they used FFP and not the FIB concentrate. Further, there was no depiction of dynamic monitoring of FIB levels during the treatment, neither the basis on which FFP dose was calculated in the case report. In a similar case, a young woman had recurrent hemoperitoneum due to bleeding at ovulation. After she took oestrogenic pills since the age of 19, no recurrence of hemoperitoneum was recorded.³²

Recently, our hospital treated a 14-year-old girl. Since her menarche at the age of 13, severe bleeding episodes occurred every 2 to 3 months. She was referred to our hospital due to an intra-abdominal hemorrhage secondary to a ruptured corpus luteum cyst. On admission, her Hb was 71 g/L, and FIB was 0.3 g/L. The patient's first bleeding episode began at 7 days after birth (prolonged umbilical hemorrhage), and she was diagnosed as congenital hypofibrinogenemia since the age of 2 years. Since her birth, the girl had frequent spontaneous bleeding symptoms, including epistaxis, othemorrhage, skin bruises, and gingival bleeding. After years of suffering, her mother even suggested a hysterectomy in consideration of subsequent unaffordable and troublesome treatment. By carefully discussing with her parents, we prescribed her with COCPs (daily intake of Marvelon for continuous 3 months, then withdrawal for 10 days, and daily intake for another 3 months). Six months after the start time, Marvelon usage changed to regular method of 21/7 days protocol as bleeding dramatically decreased and anemia cured. A Mirena was also inserted under intravenous anesthesia. Noticeably, the anesthetic effect was satisfying and the hymen was still intact after insertion of Mirena. Now the follow-up has been conducted for 8 months.

Adverse reactions included headache and skin rash, both of which have disappeared shortly. A cerebral computed tomography scan revealed normal results. The patient was recommended not to participate in physical education classes at school, and her daily life was uneventful.

Interestingly, the above 2 cases demonstrated different features. In the first case, the patient had no bleeding episode until presenting with hemoperitoneum at the age of 18. Whilst in our case, the patient had frequent severe bleeding ever since menarche. Another point to be made is the extended application for Mirena. To our knowledge, the patient in our case is the youngest Mirena user and the only virgin when Mirena was inserted worldwide. Follow-up is in process to test the long-term treating effect. Hopefully, this case will broaden our understanding and clinical application of Mirena for menorrhagia secondary to coagulation disorders.

Complications and Management in Pregnancy

Fibrinogen plays an important role in maintaining placenta integrity by supporting cytotrophoblast spreading for the development of fetal-maternal vascularization.³³ Congenital hypofibrinogenemia/afibrinogenemia complicating pregnancy is an extremely high-risk situation and often leads to unfavored pregnancy outcomes, such as bleeding in early gestations, early miscarriage, premature delivery, fetal growth restriction, placental abruption, fetal loss, postpartum hemorrhage, postpartum thrombosis, and so on.^{34,35} Currently, only a few cases are available on pregnancy associated with congenital hypofibrinogenemia/afibrinogenemia. Due to the rarity of the disease and the absences of randomized controlled studies, management of pregnancy with congenital hypofibrinogenemia/afibrinogenemia is challenging. Li and colleagues reported the perioperative management of 4 pregnant women having congenital hypofibrinogenemia scheduled for elective cesarean delivery.³⁶ Among the 4 cases, all patients were asymptomatic, whereas 1 patient had recurrent pregnancy loss (case 3), 1 had positive family history (case 2), and 2 cases demonstrated offspring heredity (cases 3 and 4). Noticeably, case 3 (all autoimmune checks are negative, thus autoimmune deficiency-induced miscarriage is excluded) had 6 early miscarriage before this pregnancy, with each fetal loss at around 8 gestational week, indicating a strong correlation between low-FIB levels and unfavored pregnancy outcome. The researchers held that the replacement therapy was essential to avoid anesthesia and obstetric complications. Thus, FIB concentrate was given to all the patients perioperatively to prevent severe hemorrhage (ranging from 2-22 g before and after the cesarean delivery to maintain a perioperative FIB level above 200 mg/dL).^{37,38} Another research also recommended a regular replacement therapy with FIB concentrates or cryoprecipitate infusions throughout pregnancy to maintain FIB levels between 500 and 1000 mg/dL in women with congenital hypofibrinogenemia/afibrinogenemia.³⁹ As for the selection of delivery modes, both vaginal delivery and cesarean delivery have been reported for

women with congenital hypofibrinogenemia/afibrinogenemia.⁴⁰⁻⁴² However, currently there is lack of evidence in which delivery mode is more superior for women with this disease. In their review, Huq and Kadir regarded planned cesarean delivery seemed to be more appropriate since prolonged labor and difficult delivery especially vacuum extraction are probably associated with the highest risk of cranial bleeding.³⁸ As for the selection of anesthesia mode, intraspinal anesthesia is in favor for the infants, whereas it has an increased incidence of epidural hematoma secondary to maternal coagulation defects. The 4 cases in Li's study were all given uncomplicated combined spinal-epidural anesthesia and underwent uneventful surgical procedure without postpartum hemorrhage, due to the adequate and in-time injection of FIB concentrate and satisfactory maintenance of plasma FIB levels perioperatively.³⁶ It is thus suggested perinatal management for patients with congenital hypofibrinogenemia/afibrinogenemia requires a multidisciplinary approach and advanced individualized management plan taking into consideration obstetric and bleeding risk factors. Patients with severe or rare disorders or carrying an affected infant should be managed in a tertiary center with an onsite blood products center.³⁸

In a larger scale study, the researchers reviewed treating experience from 11 cases with congenital hypofibrinogenemia in pregnancy at a single center.⁴³ For majority of the cases (9 in 11), hypofibrinogenemia was diagnosed by routine test in pro-gestation and in early pregnancy, and none of them showed bleeding tendency during pregnancy. Their pregnancy FIB ranged from 48 to 111 mg/dL, with 20th to 28th gestational weeks, showed the lowest FIB levels throughout pregnancy.⁴³ This is inconsistent with known maternal physiological hypercoagulative state and increased FIB levels throughout pregnancy.⁴⁴ As for the delivery mode, 8 patients underwent vaginal deliveries including 1 forceps delivery and 4 cesarean deliveries. All the 4 surgeries had clear indications, including a scarred uterus, suspected fetal macrosomia, prolonged second stage of labor, and low placenta, respectively. All the cases underwent deliveries uneventfully, with an average of gestation age of 39 weeks. The researchers attributed this satisfying outcome to the FIB replacement therapy before delivery. Since an increased prevalence of placental abruption has been reported in women with hypofibrinogenemia who did not receive FIB replacement.³³ They also drew the conclusion that cesarean delivery is not the indication in women with abnormal FIB levels. On the contrary, vaginal delivery is more beneficial for this subtype.⁴³

Researchers reported a very rare case of interstitial pregnancy in a woman with congenital afibrinogenemia in Japan.⁴⁵ A woman with congenital afibrinogenemia who had not received the recommended FIB replacement for the first 6 weeks of pregnancy had right interstitial pregnancy. Before the pregnancy, the patient received a right salpingo-oophorectomy for ovarian hemorrhage. Therefore, the embryo entered the uterine cavity via the left tube and then moved upstream to the interstitial part of the right tube. The authors held that disturbance of the embryo's decidual attachment was

a possible cause for ectopic pregnancy, thus they emphasized the importance of FIB replacement early in the first trimester.⁴⁵

Perinatal Thrombosis

Patients with congenital hypofibrinogenemia/afibrinogenemia have been reported to have had both arterial and venous thrombosis, with/without prior infusion of FIB, and with/without underlying tendencies to thrombophilia.⁴⁶ Roqué et al depicted an interesting case of congenital afibrinogenemia complicating with pregnancy-related thrombosis.¹⁶ The woman demonstrated spontaneous hemorrhage since her newborn period, with undetectable FIB levels. She had severe bleeding episodes, including splenic rupture, and a hemorrhagic corpus luteum at menarche. Combined oral contraceptive pills were prescribed for her to prevent future ovulation-associated bleeding. Conception occurred when the patient self-discontinued the COCPs. During her first pregnancy, the patient was given cryoprecipitate intermittently (generally twice a week) to keep the FIB level >60 mg/dL. At 35.6 weeks of gestation, the patient was given an emergency cesarean delivery on indications of placental abruption, which was later confirmed during the surgery. Fortunately, the infant was viable with a 10-minute APGAR score of 7. Two years later, she was pregnant again during cryoprecipitate prophylaxis, and the FIB level was again maintained >60 mg/dL. A planned cesarean delivery was performed at 34.5 weeks. Eleven days after the delivery, thrombi were detected in left renal vein and left gonadal vein. Assays of antithrombin, protein C, protein S, APCR, and tests for the lupus anticoagulant were all normal, thus concurrent thrombophilia was excluded. After 14 days treatment with unfractionated heparin and cryoprecipitate, the thrombi disappeared. By reviewing the 2 pregnancy's treatment of the same case, the authors wondered whether to maintain high levels of FIB played a role in the development of paradoxical thromboses.¹⁶ In a previous study, fibrin was found to be able to inactivate thrombin, and patients with low FIB were at risk of thrombosis due to the persistent presence of thrombin.⁴⁷ Therefore, some researchers recommended to keep the FIB level greater than 60 mg/dL and, if possible, above 100 mg/dL for pregnancy in women with congenital afibrinogenemia.⁴⁰ Besides, continuous infusion of FIB concentrate in perinatal period was also recommended to maintain FIB above 150 mg/dL or, ideally, above 200 mg/dL.⁴⁰ However, high-level replacement during pregnancy is still controversial considering the possibility of thromboembolic events.

Thrombosis in Nonpregnancy Period

The occurrence of thrombotic events in patients with congenital hypofibrinogenemia/afibrinogenemia has been already reported. Among those cases, some were in association with replacement therapy, while a few others were evidently spontaneous. Castaman et al once depicted 2 cases of severe spontaneous arterial thrombotic manifestations in women with congenital hypofibrinogenemia/afibrinogenemia.⁴⁸ Similar

findings include peripheral thrombosis in a young patient with congenital afibrinogenemia, bilateral ischemic lesions of toes and fingers in a patient with hypofibrinogenemia, thrombosis of peripheral arteries in a patient with afibrinogenemia and protein C deficiency, and so on.^{17,49,50} Postoperative deep venous thrombosis has also been reported among women with congenital afibrinogenemia.¹⁵

Ozdemir et al once reported a rare case of congenital afibrinogenemia complicated with thromboembolic events that required repeated amputations.⁵¹ The patient was a 23-year-old woman who was diagnosed with congenital afibrinogenemia since the age of 13. Bilateral ischemic lesions of bilateral foot and ankle that required amputations were depicted. The patient was treated with FIB concentrate, low-molecular-weight heparin, aspirin, and nifedipine. Based on their experience, the authors thought low-molecular-weight heparin and aspirin with FIB replacement at the same time seemed to be effective in the rare complication of thrombotic events. The authors concluded that the complication of thrombosis in patients with quantitative FIB disorders may be associated with additional risk factors such as additional thrombophilic risk factors or oversaturation of FIB after replacement therapy.

Infusion of FIB-containing products, including inactivated plasma-derived concentrates of FIB and cryoprecipitates, is the widely accepted way to maintain FIB levels in perioperative period. We would like to stress again that FIB concentrate has priority over FFP for consideration of safety.^{19,20} However, studies also indicated a possible link between the infusion of FIB-containing products and thrombosis development.¹⁵ Currently, there is no standard or consensus on the target plasma FIB levels considered adequate to control bleeding. One guideline in Japan recommended target FIB levels of 1 g/L in the perioperative period.⁴⁰ In brief, the risk of bleeding and of thromboembolic events must be balanced in these patients, and cautious monitoring of thromboembolic signs should be performed during FIB infusion treatment.

Postmenopausal Hormone Replacement Therapy and Acquired Low FIB Level

Hormone replacement therapy (HRT) is now widely used among postmenopausal women to reduce intolerable menopausal symptoms and prevent disorders such as osteoporosis and atherosclerosis. Among others, venous thromboembolic events (VTEs) is believed to be a major adverse event of HRT. A former 3-year, double-blinded, placebo-controlled trial of 875 postmenopausal women was conducted to examine potential risk factors for VTEs in women assigned to HRT.⁵² To their surprise, the researchers found that women who experienced VTEs had a significantly lower mean FIB level than those who did not ($P < .03$). This finding seems to be confusing considering that women who experienced VTEs are likely to be in a prehypercoagulable state. Recently, many studies arise to explore the relation between female hormones and FIB levels, generating inconsistent results.⁵³⁻⁵⁵ However, considering the direct and indirect effects of female hormones on coagulation

and increasingly used HRT among postmenopausal women, it is important to further explore whether there is a real association between FIB levels, HRT, VTE occurrence, and underlying mechanism.

Management in Special Conditions

Clinicians in Johns Hopkins medical center depicted the perioperative coagulation management in the first-reported patient with afibrinogenemia undergoing liver transplantation.⁵⁶ The patient's parents are first cousins, and consanguineous marriages have been reported to have increased incidence of delivering offsprings with congenital FIB deficiencies.^{37,57} The patient had intermittent severe bleeding episodes ever since 6 months old and received cryoprecipitate every 3 or 4 years for bleeding complications such as dental bleeding and menorrhagia. Directly before the transplantation surgery, an initial thrombelastogram (TEG) showed a flat line, indicating a complete lack of fibrin clot formation. A 20-U cryoprecipitate were infused just before the operation. As arterial and central access were obtained, an additional 10 U of cryoprecipitate was given. No antifibrinolytic therapy was performed throughout the perioperative period since there was no sign or symptom of hyperfibrinolysis. Inspiringly, coagulation studies normalized with the newly functioning liver, indicating good synthetic liver function. In this case, the perioperative coagulation management was mainly guided by TEG, a leading index in coagulation management during liver transplantation.⁵⁸ Thrombelastogram is also considered as a sign of hyperfibrinolysis monitored during liver transplantation and an indication for reactive therapy.⁵⁸ The authors concluded that liver transplantation could be safely performed in patients with afibrinogenemia with the supportive care of perioperative physicians.⁵⁶

Discussion and Conclusion

Congenital hypofibrinogenemia and afibrinogenemia are rare autosomal recessive bleeding disorders characterized by very low or undetectable circulating FIB due to mutations in FIB genes.⁵⁹ Mutations in FIB chain encoding genes are the most common cause for congenital FIB disorders. Dozens of different defective genetic alterations of FIB have been reported.⁵⁶ Due to their specific physiological features, female patients with this disease are more vulnerable compared with male patients, particularly during the childbearing period.

Here, we reviewed the clinical manifestations and management of congenital hypofibrinogenemia/afibrinogenemia at different life stages of female patients. Fibrinogen replacement therapy is the standard for management in these patients. Adjuvant therapy includes oral intake of COCPs, insertion of Mirena, local hemostatic measures, and lifestyle recommendations. Noticeably, many evidences indicate a potential link between replacement therapy and thrombotic events, thus a cautious monitoring of coagulation function and thrombophilia

should be well applied during application of FIB replacement products.

Authors' Note

Yan Zhang and Xiaohang Zuo contribute equally to this work. This article does not contain any studies with human participants or animals performed by any of the authors. Fibrinogen (FIB) replacement therapy is the standard for management in patients with congenital Hypofibrinogenemia/afibrinogenemia. A cautious monitoring of coagulation function and thrombophilia should be well applied during application of FIB replacement products.

Declaration of Conflicting Interests

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