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Hamostaseologie

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Abstract

Congenital afibrinogenemia and hypofibrinogenemia are rare hereditary coagulation disorders characterized by the absence or deficiency of fibrinogen. These conditions pose unique challenges for women across their lifespan, including heavy menstrual bleeding (HMB), hemorrhagic ovarian cysts, complications during pregnancy and the postpartum period, as well as bleeding occurring later in life. HMB is frequent and adversely impacts quality of life, often necessitating hormonal therapy, antifibrinolytics, or fibrinogen replacement. Hemorrhagic ovarian cysts can result in life-threatening hemoperitoneum, requiring prompt intervention to manage bleeding and preserve ovarian function. Pregnancy in women with severe fibrinogen deficiencies carries a high risk of miscarriage, placental abruption, and postpartum hemorrhage. Multidisciplinary care, fibrinogen replacement, and vigilant monitoring are crucial to optimize maternal and fetal outcomes. Although understudied in this population, bleeding can occur later in their life, especially due to the increased incidence of gynecological pathologies. Tailored management strategies, including hormonal and surgical interventions, are essential. Despite recent advances in our understanding of these conditions, significant knowledge gaps persist regarding the prevalence, risk factors, and optimal management of specific complications. This review synthesizes current findings and provides practical recommendations to guide the care of young and ageing women with afibrinogenemia and hypofibrinogenemia. Further research is needed to refine treatment protocols and improve outcomes for this vulnerable population.

Keywords

- afibrinogenemia
- hypofibrinogenemia
- miscarriage
- heavy menstrual bleeding
- pregnancy
- postpartum hemorrhage
- thrombosis
- ovarian cysts

Introduction

Fibrinogen, a hexameric glycoprotein, is composed of three polypeptide chains (α, β, and γ) that are encoded by the *FGA*, *FGB*, and *FGG* genes located on chromosome 4. Hepatocytes secrete it into the circulation, where it reaches concentrations of 1.5 to 4 g/L in healthy individuals. At the end of the coagulation cascade, thrombin cleaves fibrinopeptides A and B from the α and β fibrinogen chains, triggering the spontaneous polymerization process that ultimately forms a fibrin network.[1]

Congenital afibrinogenemia and hypofibrinogenemia are rare hereditary coagulation disorders, characterized by a deficiency in fibrinogen.[2] Afibrinogenemia is defined as the complete absence of fibrinogen, whereas hypofibrinogenemia is defined by a partial decrease.[3] More specifically, hypofibrinogenemia is classified as severe when the fibrinogen level is less than 0.5 g/L, moderate when the fibrinogen

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level is between 0.5 and 0.9 g/L, and mild when the fibrinogen level is greater than 0.9 g/L.[4] The bleeding phenotype of patients is mostly dependent on fibrinogen levels. Major bleeding occurs in afibrinogenemia and severe hypofibrinogenemia, and essentially traumatic bleeding in moderate and mild hypofibrinogenemia.[5] In an international study of 204 patients with afibrinogenemia, the median International Society of Thrombosis and Hemostasis Bleeding Assessment Tool was 14, with no differences between adult and child patients. However, umbilical and cerebral bleeding are common complications in children, reported in 48% and 31% of patients, respectively.[6,7] Furthermore, the tendency to thrombosis is a paradoxical complication of afibrinogenemia and severe hypofibrinogenemia, which highlights the complex role of fibrinogen in the coagulation cascade and the hemostasis balance.[8] A number of fibrinogen mutations have been identified in quantitative fibrinogen disorders, mainly null mutations in *FGA* and *FGB*.[9] The most prevalent mutations are the 11-kb deletion of *FGA* and the donor splice site mutation c.510 + 1G > T in *FGA*.[10]

These conditions lead to distinctive challenges for women across all life stages.[11,12] Heavy menstrual bleeding (HMB), often from menarche, is frequent and may lead to chronic anemia. Hemorrhagic ovarian cysts can cause life-threatening bleeding.[13,14] Pregnancy is a high-risk situation, with an increased incidence of miscarriage, placental abruption, and postpartum hemorrhage (PPH) in the absence of adequate fibrinogen replacement.[15] Perimenopausal and postmenopausal bleeding and bleeding due to underlying gynecological pathologies may be exacerbated by the fibrinogen deficiency.[16] Despite advances in our understanding of the epidemiology of fibrinogen disorders, the management of these clinical situations remains challenging and requires a multidisciplinary approach.

General recommendations on management of gynecological issues and pregnancy in bleeding disorders have recently been proposed by the United Kingdom Haemophilia Centre Doctors Organisation[16,17] and more detailed on fibrinogen disorders by the factor XIII and fibrinogen Subcommittee of the International Society of Thrombosis and Hemostasis.[18] Given the rarity of these conditions and the limited data available—particularly in specific subpopulations such as ageing women—more detailed, evidence-based recommendations may not yet be feasible. The current suggestions likely reflect the best available expert consensus in the absence of robust clinical studies. The objective of this review is to synthesize the findings of recent studies and recommendations and offer practical recommendations to optimize the care of women across their lifespan, from childhood to elderly years. Dysfibrinogenemia is a distinct condition that differs significantly from afibrinogenemia and hypofibrinogenemia in terms of diagnosis, genetics, clinical presentation, and management. For reasons of clarity, we have chosen to focus on afibrinogenemia and hypofibrinogenemia. For a more comprehensive overview of dysfibrinogenemia management, readers are referred to two recent expert consensus papers.[18,19]

Heavy Menstrual Bleeding

HMB represents a significant concern for women with quantitative fibrinogen disorders.[2] The prevalence of HMB is high in individuals with afibrinogenemia and severe hypofibrinogenemia, although it varies across the series.[20] In an international cross-sectional study comprising 204 patients with afibrinogenemia, 42 (73.7%) of adult women reported HMB.[21] In this study, HMB had an adverse effect on women's health-related quality of life, manifesting as limitations in daily activities, changes in social functioning, and impaired relationships.[21] Similar prevalence were reported in an Iranian cohort of 55 patients with afibrinogenemia, where 70% of women had HMB.[22] In a retrospective international study comprising 16 women with afibrinogenemia and 18 with hypofibrinogenemia of varying severity, HMB was observed in 33% of cases.[6] A retrospective analysis of data from the Rare Bleeding Disorder in the Netherlands (RBiN) study revealed that 13 out of 19 women with fibrinogen disorders experienced HMB.[23]

The management of HMB necessitates a multidisciplinary approach, integrating the expertise of hematologists, gynecologists, pediatrics, and other specialists, ideally prior to menarche.[13,24] Regular monitoring of hemoglobin, iron status, and fibrinogen levels is essential for guiding treatment adjustments and preventing complications such as anemia or uncontrolled bleeding.[25,26] The prevention of HMB begins with the administration of hormonal therapy which addresses menstrual flow.[16] Hormonal therapy, including combined oral contraceptives, progestin-only methods, or the levonorgestrel-releasing intrauterine system, provides control by suppressing or regulating menstruation.[12,27,28] In case of severe HMB, continuous or extended-cycle hormonal regimens may be employed to eliminate menstruation altogether.[29] As previously mentioned, women with afibrinogenemia and severe hypofibrinogenemia are also at risk of thrombosis. This complex dual risk must be carefully managed, when evaluating the choice of hormonal therapy in reproductive-aged women.[30] The adjunctive use of antifibrinolytic agents such as tranexamic acid may further reduce menstrual bleeding.[16,31] When hormonal and antifibrinolytics are not efficacious, fibrinogen infusion may be necessary with the aim of achieving a fibrinogen level of 1.5 g/L.[32]

Hemorrhagic Ovarian Cysts

In addition to HMB, women are at risk of hemorrhagic ovarian cysts.[2] These can be follicular or corpus luteum cysts and may present as an emergency in case of hemoperitoneum.[12,14,33–39] Hemorrhagic ovarian cysts can be a life-threatening complication, and the diagnosis may be missed due to their rarity. Moreover, as highlighted in ►Table 1, these events can occur at a young age, emphasizing the need for increased awareness among clinicians.

A retrospective study from Iran examined 210 patients with rare bleeding disorders who were suspected of having hemorrhagic ovarian cysts.[40] Following clinical and ultra-

Table 1 Cases reporting ovarian cysts and hemoperitoneum and related treatments in women with afibrinogenemia and hypofibrinogenemia

Study	Type of fibrinogen disorder	Age of first report (years)	Treatment	Comment
Schneider et al., 1981[38]	Afibrinogenemia	22	Oophorectomy	One episode
Bottini et al., 1991[33]	Afibrinogenemia	15	Removal of peritoneal blood, wedge ovary resection, ovariectomy, COC	Three episodes, including one severe with Ht 29%
Castaman et al., 1995[14]	Afibrinogenemia	14	Wedge ovary resection, removal of peritoneal blood, COC	Two episodes, without recurrence after 5 years of COC introduction
Koussi et al., 2001[39]	Afibrinogenemia	14	Conservative, COC	Monitoring by CT scan and discharged on the ninth day
Özdemir et al., 2004[34]	Afibrinogenemia	24	Conservative, wedge ovarian resection, oophorectomy, COC	Five episodes, two requiring a laparotomy
Cetinkaya et al., 2011[35]	Afibrinogenemia	24	Wedge ovarian resection, COC	Two episodes with hemorrhagic shock, one 3 months after COC stopping
Kim et al., 2015[36]	Hypofibrinogenemia	18	Wedge ovarian resection, COC	One episode with hemorrhagic shock
Wang et al., 2020[37]	Hypofibrinogenemia	14	Conservative, COC	Monitoring and discharged on the fourth day
Ramadan et al., 2020[66]	Hypofibrinogenemia	26	Conservative, COC	Monitoring and discharged on the sixth day
Zhang et al., 2020[12]	Hypofibrinogenemia	14	Conservative, COC	No recurrence after 8 months of follow-up

Abbreviations: COC, combined oral contraceptives; Ht, hematocrit.

sound examination, two of the seven women with afibrinogenemia or hypofibrinogenemia (with a median age of 15 years) were diagnosed with an ovarian hemorrhagic cyst.

Hormonal therapy, by inhibiting ovulation, is the first option to decrease the risk of developing hemorrhagic ovarian cysts.[14] The oral contraceptive should ideally be prescribed continuously in order to prevent menstruation as well as ovulation.[29] Hemoperitoneum is a life-threatening bleeding that requires emergency management. Several approaches have been described, including laparoscopy or laparotomy to evacuate the hemoperitoneum, ovarian cystectomy, or even oophorectomy.[14,33–36,38] A conservative management approach has also been reported with success, especially in hypofibrinogenemia.[12,37]

Pregnancy

The management of pregnancy in women with afibrinogenemia and hypofibrinogenemia necessitates a multidisciplinary approach at every stage, from preconception to delivery, in order to mitigate the increased risks of obstetric complications, bleeding, and thrombosis. The following sections outline some key steps and offer practical recommendations for their management.

Preconception Counseling

It is recommended that women with afibrinogenemia and hypofibrinogenemia undergo comprehensive preconception counseling.[18] This entails an assessment of the patient's personal and family history of bleeding, a determination of the patient's basal fibrinogen levels, and a discussion of the potential risks associated with pregnancy, including those related to bleeding, obstetrics, and thrombosis.[41] A frequent question pertains to the potential risks of miscarriage in cases of afibrinogenemia and hypofibrinogenemia. Optimizing fibrinogen levels through replacement therapy prior to conception or during the early stages of pregnancy has been demonstrated to reduce the risk of pregnancy loss and facilitate safer maternal outcomes in women with afibrinogenemia and severe hypofibrinogenemia.[42] In women with mild to moderate hypofibrinogenemia, the risk of miscarriage is likely to be similar to or slightly elevated relative to the general population. The FibrinoGEST Study, an international multicentric study involving 149 pregnancies in women with hypofibrinogenemia, revealed that 106 (71.1%) women had a live birth, 18 (12.1%) had an early miscarriage, and 2 (1.3%) had an intrauterine fetal death.[15] Similarly, a retrospective study involving 16 pregnancies in hypofibrinogenemia documented 3 miscarriages (14%).[6]

Another frequent question concerns the risk of having a child affected by the same fibrinogen disorder. Genetic counseling is a crucial element of preconception planning for women with afibrinogenemia or hypofibrinogenemia, as the biological and clinical phenotype of these conditions is inherited in an autosomal recessive and dominant pattern, respectively.[43] In the event that both parents are heterozygous carriers of the mutated gene (i.e., hypofibrinogenemia), there is a 25% probability that their offspring will inherit two copies of the mutated gene (i.e., afibrinogenemia); a 50% probability that their offspring will inherit one copy (i.e., hypofibrinogenemia); and a 25% probability that their offspring will not inherit any mutations. In the event that only one parent is a carrier of afibrinogenemia or hypofibrinogenemia, there is a 50% and 25% probability, respectively, that the child will manifest hypofibrinogenemia. This knowledge enables prospective parents to make informed decisions, including the utilization of prenatal genetic testing or preimplantation genetic diagnosis in cases of in vitro fertilization.[44] Furthermore, genetic counseling offers the chance to educate family members about neonatal risks. Finally, the autosomal inheritance of severe forms is more prevalent in populations where consanguineous marriage often occurs. The presence of language barriers can further impede access to genetic counseling and health care services, highlighting the need for culturally and linguistically appropriate counseling approaches.

Antenatal Care

Fibrinogen replacement is mandatory to support placental implantation and maintain pregnancy to term in women with afibrinogenemia and severe hypofibrinogenemia.[45] Despite limited data, there is strong evidence supporting the efficacy of fibrinogen replacement during pregnancy.[42,46–53] The minimal trough fibrinogen level remains undetermined; however, there is a consensus among experts that levels higher than 1 g/L should be targeted.[17,18,54] Generally, this target can be achieved by the infusion of 50–75 mg/kg of fibrinogen concentrate once or twice a week. The replacement regimen depends on individualized pharmacokinetics, but also on logistics aspects such as the venous access, the adherence to fibrinogen prophylaxis, and the accessibility to fibrinogen concentrates. As pregnancy progresses, there is an increase in fibrinogen clearance, which consequently necessitates an increase in the frequency of fibrinogen infusions.[47] Therefore, a monthly fibrinogen assessment is recommended.[18]

In women with mild and moderate hypofibrinogenemia, there is an increase of fibrinogen levels throughout the pregnancy, sometimes reaching "normal" fibrinogen levels.[55,56] Thus, fibrinogen replacement therapy is generally not indicated, except in case of vaginal bleeding or placenta abruption.[57,58] In the FibrinoGEST study, 7/149 (4.7%) pregnancies in women with hypofibrinogenemia were complicated by vaginal bleeding and 12/149 (8%) by retroplacental and placental abruption.[15]

Delivery

For women with afibrinogenemia and severe hypofibrinogenemia, delivery must be planned in coordination with the blood bank, the laboratory, and the multidisciplinary clinical team, including obstetricians, hematologists, anesthesiologists, and neonatologists.[18] Regardless of the delivery modality, fibrinogen replacement is necessary to achieve a peak fibrinogen level higher than 1.5 g/L. It is imperative to avoid the utilization of forceps, ventouse, fetal blood sampling, and fetal scalp electrodes when the infant is at risk of severe fibrinogen deficiency.[17] In mild to moderate hypofibrinogenemia, fibrinogen levels often spontaneously reach 1.5 g/L at term. In that case, spontaneous delivery is allowed.

Central neuraxial anesthesia should be avoided in women with fibrinogen levels below 1.5 g/L. Despite the fact that this procedure can be safely performed when fibrinogen levels are adequately substituted,[59] neuraxial anesthesia is not frequently offered to women with fibrinogen disorders due to concerns of bleeding complications. In the FibrinoGEST Study, one-third of the deliveries ($n = 29$, 29%) were managed without anesthesia due to the underlying hypofibrinogenemia.[15]

Postpartum

PPH is a frequent complication. The RBiN study reported detailed data on 40 deliveries from 13 women with hypofibrinogenemia of various severities. Overall, 21 (35%) were complicated by PPH, without differences among patients receiving a fibrinogen prophylaxis or not.[60] A similar finding was reported in the FibrinoGEST Study, which documented 19 (18.2%) cases of PPH following 106 deliveries.[15] Therefore, close clinical and biological monitoring is necessary after birth, and early fibrinogen supplementation and antifibrinolytic agents should be prescribed in case of bleeding.

The pregnancy and the delivery may confer a significant thrombotic risk factor, especially in women receiving cryoprecipitate as prophylaxis.[50,61] Consequently, it is imperative to discuss the administration of adequate fibrinogen substitution and thromboprophylaxis during the assessment of delivery and postpartum care plans.[18] In case of fibrinogen replacement, the administration of low-molecular-weight heparin as pharmacologic thromboprophylaxis is recommended until the patient is discharged. The extension of thromboprophylaxis to 4 to 6 weeks on fibrinogen prophylaxis may be considered depending on the patient's clinical phenotype and other thrombotic risk factors.[2,18]

Ageing Women

There are no data evaluating the prevalence of bleeding in ageing women with afibrinogenemia and hypofibrinogenemia. However, it is expected that the prevalence will be similar to that in women with severe von Willebrand disease or hemophilia.[62,63] With fibrinogen replacement, life expectancy in women with afibrinogenemia and severe hypofibrinogenemia can be expected to approach normal, while women with mild to moderate hypofibrinogenemia generally have a normal life expectancy. As women with fibrinogen disorders age, they may face an elevated risk of bleeding related to late gynecological issues, including menopausal and postmenopausal complications. Clinicians managing women with afibrinogenemia or hypofibrinogenemia should, therefore, remain vigilant for symptoms of menopausal (increased HBM due to anovulatory

cycles) and postmenopausal bleeding, especially in the presence of acquired gynecological pathologies. Prompt evaluation is essential to rule out serious underlying causes such as endometrial hyperplasia, fibroids, or gynecological malignancies,[64] as well as to manage any potential complications related to excessive bleeding.[65] Treatment strategies typically involve a multidisciplinary approach. Therapeutic options may include fibrinogen replacement therapy, hormonal regulation, considering the thrombotic risk, or surgical interventions such as hysteroscopy or endometrial ablation, depending on the severity of symptoms and underlying pathology. Given the lack of specific studies on this subgroup, further research is warranted to better understand the prevalence, risk factors, and optimal management of postmenopausal bleeding in women with fibrinogen disorders.

Conclusion

Women with congenital afibrinogenemia and hypofibrinogenemia encounter substantial health challenges related to bleeding and thrombosis, necessitating comprehensive, multidisciplinary care across all life stages. Individualized management strategies are imperative in addressing bleeding risks in case of HMB, hemorrhagic ovarian cysts, pregnancy complications, and bleeding occurring later in life. While current guidelines provide a framework for care, substantial gaps in knowledge, particularly regarding ageing women, underscore the necessity for further research. Consequently, ongoing studies and enhanced collaboration between hematologists and gynecologists are imperative to optimize outcomes and enhance quality of life for affected women.

Conflict of Interest

AC reports grants and fees paid to his institution from Sobi, Takeda, LFB, and Novo Nordisk; and has participated in advisory boards for Sobi.

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