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RECOMMENDATIONS AND GUIDELINES

Management of pregnancy and delivery in congenital fibrinogen disorders: communication from the ISTH SSC Subcommittee on Factor XIII and Fibrinogen

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Abstract

Congenital fibrinogen disorders (CFDs) are a heterogeneous group of rare congenital quantitative and/or qualitative fibrinogen deficiencies. The spectrum of molecular anomalies is broad, leading to several subtypes of fibrinogen disorders (ie, afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia). Pregnancy in women with CFDs is a high-risk clinical situation, with an increased tendency for miscarriages, bleeding, and thrombosis. Even though it is well established that management of such pregnancies requires a multidisciplinary approach involving specialists (hematologists and maternal/fetal medicine experts with expertise in the management of inherited bleeding disorders), specific guidelines are lacking. In this International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee communication, we aim to propose an expert consensus opinion with literature evidence where available on the strategy for management of pregnancy, delivery, and puerperium in CFDs.

KEYWORDS
afibrinogenemia, congenital, fibrinogen, fibrinogen deficiency, hypofibrinogenemia, pregnancy

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1 | INTRODUCTION

Congenital fibrinogen disorders (CFDs) encompass a broad spectrum of fibrinogen disorders, including afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia [1]. Afibrinogenemia is defined by the complete absence of fibrinogen in circulation and hypofibrinogenemia by decreased levels of functional fibrinogen. Dysfibrinogenemia and hypodysfibrinogenemia are characterized by normal and decreased levels of dysfunctional fibrinogen, respectively. The Factor XIII and Fibrinogen Scientific and Standardization Committee (SSC) has classified these subtypes based on genotype, fibrinogen level, and clinical phenotype (Table 1) [1].

Although clinical symptoms are heterogeneous, depending on the type and subtype of CFD, pregnancy complications are well documented [2]. It has been reported that pregnant women with CFD may be at risk for miscarriages [3], vaginal bleeding [4], placental abruption [5], postpartum hemorrhage (PPH) [6], and thromboembolic events [7], but epidemiologic data are scarce [8]. In many cases, management of delivery required fibrinogen replacement for safe neuraxial anesthesia, and on occasion, tranexamic acid (TXA) was also used in the postpartum period to reduce bleeding risk. However, formal guidelines are lacking, and the level of available evidence is very low. The aim of this SSC communication is to propose suggestions on the strategy for management of pregnancy, delivery, and puerperium in CFDs based on expert consensus opinion in full agreement by all authors and available literature review. In order to decrease redundancy in the text, we decided not to provide specific recommendations for hypodysfibrinogenemia. Most of the suggestions given for hypofibrinogenemia and dysfibrinogenemia can be applied to hypodysfibrinogenemia according to the clinical phenotype (bleeding, thrombosis, or both) and fibrinogen levels.

TABLE 1 ISTH classification of congenital fibrinogen disorders adapted from Casini et al. [1].

Type and subtypes	Description
1. Afibrinogenemia	
1A. Afibrinogenemia	Patients either with a bleeding phenotype or asymptomatic individuals
1B. Afibrinogenemia with a thrombotic phenotype	Patients with a thrombotic phenotype
2. Hypofibrinogenemia	
2A. Severe hypofibrinogenemia	Activity fibrinogen level <0.5 g/L
2B. Moderate hypofibrinogenemia	Activity fibrinogen level between 0.5 and 0.9 g/L
2C. Mild hypofibrinogenemia	Activity fibrinogen level between 1 g/L and lower limit of normal value
2D. Hypofibrinogenemia with fibrinogen storage disease	Familial hypofibrinogenemia with histologically proven accumulation of fibrinogen in hepatocytes
3. Dysfibrinogenemia	
3A. Dysfibrinogenemia	Patients either with bleeding phenotype or with thrombotic phenotype not fulfilling criteria for dysfibrinogenemia 2B or asymptomatic individuals
3B. Thrombotic-related dysfibrinogenemia	Patients carriers of a thrombotic fibrinogen mutation[a] or suffering from thrombotic events with a first-degree familial thrombotic history (relatives with the same genotype) without any other thrombophilia
4. Hypodysfibrinogenemia	
4A. Severe hypodysfibrinogenemia	Antigenic fibrinogen level <0.5 g/L
4B. Moderate hypodysfibrinogenemia	Antigenic fibrinogen level between 0.5 and 0.9 g/L
4C. Mild hypodysfibrinogenemia	Antigenic fibrinogen level between 1 g/L and lower limit of normal value

[a] Fibrinogen Dusart, Fibrinogen Caracas V, Fibrinogen Ijmuiden, Fibrinogen New York I, Fibrinogen Nijmegen, Fibrinogen Naples at homozygous state, Fibrinogen Melun.

2 | GENERAL SUGGESTIONS

As a rule, all women with known CFDs or diagnosed during pregnancy should be managed by a multidisciplinary team (MDT), including anesthetists, hematologists, neonatologists, and obstetricians experienced in the field of rare bleeding disorders, preferably affiliated with a bleeding disorder center. Preconception genetic counseling should be provided for every woman with a desire to bear children. Baseline (prepregnant) fibrinogen level, clinical phenotype, and genetic mutation, if available, should be documented.

Taking into account the personal and family history of past pregnancies and bleeding/thrombotic complications, the MDT should discuss i) implications of genetic screening, inheritance, and risk of transmission to the baby; ii) potential pregnancy and postpartum complications (miscarriages, pregnancy loss, other obstetric complications, as well as bleeding and thrombotic risks); iii) therapeutic plan for the antenatal period with fibrinogen replacement, and/or low-molecular-weight heparin (LMWH); and iv) management of labor and delivery including modalities of delivery, neuraxial block, and plan to minimize bleeding and thrombotic complications in the peripartum and postpartum periods [9]. During the third trimester of pregnancy, we recommend that a personalized birth plan for mother and child with a multidisciplinary approach for delivery and peripartum is formulated and made available for all health care professionals involved in the care of the woman [10,11]. Whenever possible, delivery should be scheduled in hospitals with support from a bleeding disorder center.

For neuraxial block, we suggest an individualized assessment in advance of the delivery date (early third trimester) by the MDT and

discussion with the mother about benefits and risks of this option [9,12–14], with a clear plan on whether and how this option can be offered.

Although PPH in women with CFDs can be due to or exacerbated by their coagulation defect, obstetric causes of PPH should not be overlooked. Therefore, the peripartum plan should include active management of labor, liberal use of uterotonics to minimize risk of uterine atony, as well as prevention, early recognition, and management of birth canal trauma and placental retention. PPH management requires initiation of massive transfusion protocols and use of treatment protocols for the general population, including early administration of TXA and adequate fibrinogen replacement. When using fibrinogen concentrates, we suggest the following formula for evaluating the amount of fibrinogen to administer: (target fibrinogen activity [g/L] – measured fibrinogen activity by the Clauss method [g/L]) x (1/incremental recovery) x body weight (kg). One unit of cryoprecipitate (15-20 mL) contains 100 to 250 mg of fibrinogen; thus, 1 unit of cryoprecipitate per 5 kg of patient weight increases fibrinogen activity by about 1 g/L (number of bags to infuse: 0.2 x weight [kg]). The standard preparation of fresh frozen plasma contains 2.0 g/L (range, 0.9-3.2 g/L) fibrinogen (equivalent to 0.6 g in a 300 mL unit) [15].

When indicated, pharmacologic thromboprophylaxis should be managed with LMWH.

3 | WOMEN WITH AFIBRINOGENEMIA AND HYPOFIBRINOGENEMIA (TABLE 2)

3.1 | Prepregnancy care

When both parents are heterozygous for a hypofibrinogenemic mutation (ie, having 25% chance of having a child with afibrinogenemia with potentially severe bleeding phenotype), risk and modalities of an invasive prenatal diagnosis, such as chorionic villus sampling or amniocentesis under fibrinogen replacement, should be discussed to assist assessment of fetal bleeding risks related to the delivery and plan mode of delivery [16].

Given the high risk of miscarriage in women with afibrinogenemia and severe hypofibrinogenemia, fibrinogen replacement starting preconception must be discussed.

3.2 | Antenatal care

If a prenatal diagnosis is planned, a fibrinogen replacement is necessary for afibrinogenemia and hypofibrinogenemia (with fibrinogen levels <1.5 g/L) to target a fibrinogen level of 1.5 g/L timed before the invasive procedure.

In women with afibrinogenemia and severe hypofibrinogenemia, given the high rate of spontaneous abortion prior to 8 weeks, fibrinogen replacement must be continued or started soon after conception and pregnancy confirmation, targeting a trough fibrinogen level of ≥1 g/L throughout the pregnancy (if this is difficult to achieve, especially with fresh frozen plasma, target 0.5-1 g/L during the 2 first trimesters) [7,13,17]. In women with mild and moderate hypofibrinogenemia, fibrinogen replacement targeting a trough fibrinogen level of ≥1 g/L throughout the pregnancy is suggested to avoid risk of placental abruption [18].

We recommend weekly trough fibrinogen measurements in the first month after initiating fibrinogen replacement and then monthly to maintain target levels [19]. If using a plasma-derived fibrinogen concentrate, a pharmacokinetic study to tailor dosing and maintain target trough levels is recommended. In afibrinogenemia, an increase in fibrinogen dose requirement is expected throughout the pregnancy due to the increased fibrinogen clearance necessitating bi/triweekly fibrinogen replacement based on trough levels, at times requiring use of a central venous catheter [19]. If adaptations are needed due to thrombosis risk, it is recommended to increase administration frequency rather than the dose. In hypofibrinogenemia, a physiological increase in fibrinogen concentration could be observed from the second or third trimesters onward [20].

TABLE 2 Suggestions for management of women with afibrinogenemia and hypofibrinogenemia during pregnancy.

Pregnancy stage	Suggestions for management
Prepregnancy care	• Provide genetic counseling • Start preconceptional fibrinogen replacement[a]
Antenatal care	• Weekly fibrinogen measurements in case of initiating fibrinogen replacement and then monthly to maintain target levels • Target a trough fibrinogen level of ≥1 g/L throughout the pregnancy[b] • Fibrinogen replacement targeting fibrinogen level ≥1.5 g/L in case of vaginal bleeding • Thromboprophylaxis is the same as for the general population, with adjustment in fibrinogen replacement depending on the patient's bleeding phenotype and previous obstetric history[a]
Labor and delivery	• Keep fibrinogen level ≥1.5 g/L in case of vaginal delivery or cesarean section • Fibrinogen level ≥1.5 g/L is required for neuraxial anesthesia
Postpartum	• Clinical monitoring for 72 h • Early administration of fibrinogen replacement and tranexamic acid in case of postpartum bleeding • In women under fibrinogen prophylaxis, consider thromboprophylaxis at least until discharge[c]
Neonatal care	• When a child with afibrinogenemia is suspected, delay elective procedures until diagnosis

[a] Not mandatory in mild and moderate hypofibrinogenemia.
[b] If adaptation is needed, modify the administration frequency rather than the dose.
[c] Extension to 4 to 6 weeks after birth may be considered in women under fibrinogen prophylaxis and additional thrombotic risk factors.

In case of vaginal bleeding or placental abruption, fibrinogen replacement should be increased to target a trough fibrinogen level of ≥1.5 g/L.

In women with afibrinogenemia type 2B (ie, bleeding and thrombotic phenotype) and severe hypofibrinogenemia with a personal history of thrombosis, a pharmacologic thromboprophylaxis should be administered according to recommendations for the general population, with adjustment in fibrinogen replacement depending on the patient's bleeding phenotype and previous obstetric history [7]. In women with moderate hypofibrinogenemia, if pharmacologic thromboprophylaxis is indicated, fibrinogen replacement should be considered if fibrinogen levels are <1 g/L, especially in women with a bleeding phenotype. In women with mild hypofibrinogenemia (≥1 g/L to the lower range of reference) on thromboprophylaxis, fibrinogen replacement is generally not needed.

Due to a high risk of pregnancy loss and obstetric complications, serial ultrasound can be considered, recognizing that serial ultrasounds may not predict or diagnose early placental abruption.

3.3 | Labor and delivery

In women with afibrinogenemia and severe or moderate hypofibrinogenemia with fibrinogen levels <1.5 g/L in the third trimester, vaginal or cesarean section delivery should be scheduled with the availability of clinical expertise, laboratory, and blood bank support. In women with mild hypofibrinogenemia, spontaneous labor, and vaginal delivery should be allowed whenever possible. We suggest monitoring fibrinogen levels throughout the delivery (at time of labor and every 12 or 24 hours, depending on local resources) to maintain fibrinogen levels of ≥1.5 g/L. For cesarean section, we suggest keeping fibrinogen levels at ≥1.5 g/L based on limited expert hematology and obstetrics consensus [21]. In addition to fibrinogen replacement, in women with a bleeding phenotype, we suggest use of TXA for prophylaxis at the time of delivery.

When the baby is suspected to have afibrinogenemia or severe or moderate hypofibrinogenemia, we suggest avoiding invasive fetal procedures, ie, fetal scalp monitoring and forceps- or vacuum-assisted delivery, with early recourse to cesarean section, especially if the second stage of labor is prolonged.

3.4 | Postpartum

We suggest a close clinical observation and monitoring of postpartum fibrinogen levels targeting fibrinogen level ≥1.5 g/L for 3 days after vaginal delivery and 5 days after cesarean section [22]. To prevent secondary PPH and prolonged or heavy lochia, TXA may be considered depending on the thrombotic risk [3].

When on fibrinogen replacement, we suggest pharmacologic thromboprophylaxis with LMWH until discharge, especially in case of additional thrombotic risk factors [23]. Extension of thromboprophylaxis to 4 to 6 weeks on fibrinogen prophylaxis may be considered depending on the patient's phenotype and other thrombotic risk factors [24].

3.5 | Neonatal care

In a child with suspected afibrinogenemia or severe hypofibrinogenemia, we suggest collaboration between the neonatal and pediatric bleeding disorder teams, starting with a fibrinogen level drawn from umbilical cord blood reflective of the baby's fibrinogen. We suggest delaying elective invasive procedures (eg, venipuncture and circumcision) until a diagnosis is confirmed.

3.6 | Pregnancy loss

Once the determination has been made that the pregnancy has ended, we suggest surgical management in afibrinogenemia and severe hypofibrinogenemia to avoid excessive bleeding. In such cases, we recommended fibrinogen replacement targeting fibrinogen level ≥1.5 g/L for 3 days and TXA depending on the thrombotic risk. For mild and moderate hypofibrinogenemia without bleeding history, a spontaneous expulsion can be considered with TXA administration [3].

4 | WOMEN WITH DYSFIBRINOGENEMIA (TABLE 3)

4.1 | Prepregnancy care

Parents should be informed and counseled about inheritance and risks during pregnancy and formulate a management plan considering clinical phenotype and obstetric history. Prenatal diagnosis is deferred since it does not add to management guidelines.

4.2 | Antenatal care

Fibrinogen replacement is not routinely recommended. In cases of recurrent miscarriages or placental insufficiency without obvious causes, fibrinogen replacement targeting a fibrinogen level ≥1 g/L may be considered [25,26]. Addition of thromboprophylaxis or aspirin should be reserved, weighing risk vs benefit [6].

We recommend a quarterly assessment of fibrinogen activity level and, if available, fibrinogen antigen level [15]. A systematic monitoring of fetal growth in dysfibrinogenemia type 3B (thrombotic-related variants) is suggested [5].

For vaginal bleeding during pregnancy, fibrinogen replacement should be instituted, targeting fibrinogen level ≥1.5 g/L until cessation of bleeding [15].

In women with dysfibrinogenemia type 3B, thromboprophylaxis should be started at the beginning of gestation after pregnancy confirmation. In all other dysfibrinogenemias, thromboprophylaxis

TABLE 3 Suggestions for management of women with dysfibrinogenemia during pregnancy.

Pregnancy stage	Suggestions for management
Prepregnancy care	• Provide genetic counseling
Antenatal care	• Fibrinogen replacement is not mandatory • Quarterly assessment of fibrinogen activity level and, if available, of fibrinogen antigen level • Fibrinogen replacement targeting fibrinogen level ≥1.5 g/L in case of vaginal bleeding • Thromboprophylaxis in case of dysfibrinogenemia type 3B[a]
Labor and delivery	• Keeping fibrinogen level ≥1.5 g/L in case of vaginal delivery in women with a bleeding phenotype[b] • Keeping fibrinogen level ≥1.5 g/L in case of cesarean section • Fibrinogen level ≥1.5 g/L is required for neuraxial anesthesia
Postpartum	• Clinical monitoring for 72 h in women with a bleeding phenotype • Early use of fibrinogen replacement and tranexamic acid in case of postpartum bleeding • Thromboprophylaxis is the same as for the general population[c]
Neonatal care	• Screening for dysfibrinogenemia in the newborn is not suggested

[a] For other dysfibrinogenemia, thromboprophylaxis recommendations are the same as for the general population.
[b] Women with a personal history of significant bleeding (eg, requiring medical intervention).
[c] Patients with dysfibrinogenemia type 3B should receive thromboprophylaxis for 6 weeks after birth.

should be administered according to recommendations for the general population. Fibrinogen replacement is not necessary with concomitant thromboprophylaxis.

4.3 | Labor and delivery

In women with fibrinogen levels <1 g/L in the third trimester, we suggest a scheduled delivery with availability of laboratory and blood bank support. In women with third-trimester fibrinogen levels ≥1 g/L, spontaneous labor and vaginal delivery could be allowed where possible, although a scheduled delivery is preferred, specifically with a bleeding history. At labor, fibrinogen replacement is suggested for a woman with a bleeding phenotype targeting fibrinogen levels of ≥1.5 g/L. For neuraxial anesthesia, we suggest monitoring fibrinogen levels throughout the delivery to maintain a fibrinogen level of ≥1.5 g/L (also see section 2, General suggestions). For cesarean section, we suggest keeping fibrinogen level at ≥1.5 g/L based on limited expert hematology and obstetrics consensus [21].

If the fetus is suspected to be affected with a bleeding phenotype, as for afibrinogenemia and hypofibrinogenemia, we suggest avoiding invasive fetal procedures, ie, fetal scalp monitoring and forceps- or vacuum-assisted delivery, with early recourse to cesarean section, especially if prolonged labor is expected.

4.4 | Postpartum

We suggest monitoring postpartum fibrinogen level with early replacement targeting >1.5 g/L and TXA administration in case of bleeding. In women with a bleeding phenotype, we suggest close clinical monitoring for 72 hours [27].

Thromboprophylaxis is indicated for 6 weeks after birth in dysfibrinogenemia 3B. In other dysfibrinogenemias, we suggest thromboprophylaxis recommendations similar to those for the general population, independent of the fibrinogen levels. In women with a bleeding phenotype, mechanical prophylaxis is preferred.

4.5 | Neonatal care

Screening for dysfibrinogenemia is not suggested at birth, except in case of bleeding symptoms or surgery. Genetic testing is usually offered later in childhood.

4.6 | Pregnancy loss

Once the determination has been made that the pregnancy has ended, we suggest surgical management in dysfibrinogenemia with a bleeding phenotype to avoid excessive bleeding. In such cases, we recommended fibrinogen replacement targeting fibrinogen level ≥1.5 g/L for 3 days and TXA depending on the thrombotic risk. For dysfibrinogenemia without history of bleeding, a spontaneous expulsion can be considered.

AUTHOR CONTRIBUTIONS

A.C. drafted the manuscript, and all other authors provided intellectual input for revisions of the draft. All authors approved the final version of the manuscript.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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