

Challenges Regarding the Management of Gynecological and Obstetric Complications in Women with Inherited Factor XIII Deficiency

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Abstract

Women with rare bleeding disorders (RBDs) can be exposed throughout their life to several complications such as menorrhagia or hemorrhagic complications during pregnancies and deliveries. Among RBDs, factor XIII deficiency leads to life-threatening hemorrhages such as intracranial hemorrhage, and women during their reproductive period may experience gynecological and obstetric complications, and more specifically recurrent miscarriages due to the role of FXIII in placenta attachment. Because of the rarity of the disease, recommendations for the treatment are mainly based on expert consensus, and although the effectiveness of as-early-as-possible FXIII prophylaxis administration is largely recognized to prevent recurrent miscarriages, the dosage of this prophylaxis is still debated.

Keywords: Inherited factor XIII deficiency; Menorrhagia; Miscarriages; Pregnancy outcome

Introduction

The medical care of patients with inherited bleeding disorders requires a greater understanding and attention, especially in women who can be exposed to specific hemorrhagic complications such as menorrhagia or complications during pregnancies and deliveries. These potential complications have to be taken into account, and specific procedures or treatment regimens must be provided. Among the general population with bleeding disorders, hemophilia A and B along with von Willebrand disease represent about 95% to 97% of cases. The remaining disorders, called rare bleeding disorders (RBDs), are due to fibrinogen, or factor II, V, VII, X, XI, or XIII (FXIII) deficiencies [1]. Among these RBDs, the congenital FXIII deficiency (FXIIID) is a very rare life-threatening autosomal recessive bleeding disorder and also a cause of recurrent miscarriages. Due to the rarity of these diseases and the consequent absence of randomized controlled studies investigating treatment, recommendations for their management are mainly based on expert consensus rather than on evidence-based guidelines [2]. Since 2012, the European Network and the United Kingdom Haemophilia

Centre Doctors' Organization (UKHCDO) have published recommendations for the management of RBDs, including the management of FXIIID [3-5]. In parallel, other authors published specific recommendations regarding FXIIID treatment [6,7].

This review aimed to focus on the management of FXIIID in women. For this purpose, we searched PubMed using medical subject headings RDS(s), inherited FXIII deficiency, women, prophylaxis. All articles written in English language, and any pertinent references in these articles were reviewed. In order to improve the understanding of this rare disease, the physiological role of FXIII and the prevalence and clinical manifestations of FXIIID were described. From recent data, the treatment options to prevent the specific complications associated with FXIIID in women were detailed.

Physiological Role of FXIII in Pregnancy

FXIII is involved in hemostasis by increasing the resistance of clots and FXIIID leads to life-threatening bleeding risk [8]. FXIII is a plasmatic protein circulating

as a tetramer comprised of two A-chains (FXIII-A) and two B-chains (FXIII-B). Two separate genes (*F13A1* and *F13B*) located on different chromosomes are responsible for the production of FXIII [9,10]. Hereditary FXIII deficiencies can affect the A or B subunit, and the International Society for Thrombosis and Haemostasis (ISTH) has devised a classification based on deficiency type: subunit A deficiencies can be quantitative (type I) or functional (type II), whereas subunit B deficiencies can only be quantitative and their clinical presentation is less severe [11].

FXIII is also involved in maintaining pregnancy but its role is not completely understood. FXIII may play a role in placental attachment and is considered as essential for maintaining pregnancy [8,12-14]. FXIII is not essential to become pregnant; it has been reported that FXIII-knockout mice can initiate pregnancies, however these died prematurely due to vaginal bleeding concomitant with massive placental hemorrhage [15]. The embryos did not exhibit any abnormality, suggesting a maternal origin to these miscarriages. Some authors have proposed a role for FXIII in the Nitabuch's layer, located between the zona compacta and zona spongiosa, which constitutes the separating line at the time of delivery. By its action on the major components of the layer (fibrin and fibronectine), FXIII activity would participate in the maintenance of the integrity of this layer [16,17]. Moreover, the Nitabuch's layer would be involved in immune tolerance and FXIIID could disrupt this function and participate in fetal losses [8].

Prevalence and Clinical Manifestations of FXIII Deficiency

The prevalence of FXIIID varies around the world. One in every 1-2 million live births is affected, and the prevalence is higher among consanguineous families [6,14]. In Europe, a registry based on 13 centers outside France has identified 42 FXIII-deficient patients [5]; in France, among the 476 patients with RBDs registered on the FranceCoag Network, 33 patients present a severe FXIIID (<10 IU dL⁻¹) [18]. Signs of FXIIID range from life-threatening bleeding, such as intracranial haemorrhage (ICH), to milder forms, such as skin bleeding [5]. The minimal FXIII activity level described to prevent major spontaneous bleeds is 15 IU dL⁻¹ [19]. Umbilical cord bleeding is a frequent finding, occurring in 80% of cases, and the incidence of ICH has been reported to be 25-30%. [14]. During the reproductive period of life, women with severe FXIIID may experience an increased risk of bleeding during menstruation, pregnancy, and delivery, as well as frequent miscarriages [20]. Nevertheless, few published data are available on gynecological issues and/or obstetric complications in FXIIID women.

Regarding menorrhagia in these patients, the RBDs

Database international registry reports menometrorrhagia in women with levels of FXIII around 2.6 IU dL⁻¹ (0-23.7 IU dL⁻¹) [5]. A retrospective French series conducted in 11 women provided the largest series from Western countries of gynecological issues in patients with severe FXIIID (levels < 10 IU dL⁻¹) [21]. In this series, only 2 of the 11 patients (18%) under prophylaxis reported menorrhagia, whereas 3 (27%) women reported not experiencing menorrhagia before initiating treatment; no life-threatening peritoneal bleeding was observed [21]. The low rate of gynecological bleeding could be explained by the long-term prophylaxis treatment received by the patients; for example, in women without prophylaxis, the occurrence of menorrhagia reported ranges from 35% in 20 women in the series from Iran [22] to 63% in 11 women in a review [23]; a larger systematic review, however, found that only 31 (26%) of 121 women described with FXIIID, presented menorrhagia or heavy menstrual bleeding (HMB), and peritoneal bleeding due to ruptured ovarian cyst was reported in 10 (10%) women [20].

Regarding miscarriages, Sharief et al. report that, in 121 women with FXIIID, the risk of miscarriages was very high, nearly 70% [20]. Without FXIII substitution, the frequency of pregnancy with birth of a healthy infant was estimated to be 10%, and miscarriages occurred mainly during the first trimester [20]; a high risk of miscarriage was also the main feature of pregnancies in women with FXIIID in the French study: 30 miscarriages in 4 patients, including 12 in one patient who did not receive FXIII substitution before or during pregnancies [21], and 97% of these miscarriages occurred during the first trimester. These results are similar to those published by Naderi et al. who reported 17 cases in Iran [7].

Treatment Options for Gynecological and Obstetric Complications in Women

It is currently accepted that long-term prophylaxis should be offered as soon as possible to all patients with severe deficiency, defined as presenting severe bleeding and FXIII activity less than 15 IU dL⁻¹. A primary prophylaxis is recommended to prevent ICH [18,24]; notably, the use of high half-life *in vivo* FXIII concentrates (11 to 14 days) should be considered as it allows relatively spaced out administrations [4,18]. Two pharmacological options are available for the prophylactic or therapeutic management of severe FXIIID according to the country: a plasma-derived concentrate (pdFXIII) called Fibrogammin® (CLS Behring, Marburg, Germany) and a recombinant concentrate (rFXIII) called NovoThirteen® (Novo Nordisk HealthCare AG, Switzerland). The latter, has been approved for prophylaxis with hereditary FXIII-A deficiency [25,26]. However, the minimal FXIII activity level required to prevent spontaneous or post-surgical bleeding or miscarriage remains controversial [19,27,28].

Menorrhagia is rarely an indication for prophylaxis, but in order to prevent ICH and also menorrhagia, early prophylaxis is strongly recommended [18,29]. Although, the effectiveness of prophylactic treatment to prevent miscarriages has been reported by several authors, the minimal FXIII level required to prevent miscarriages is still debated. Some authors have recommended maintaining FXIII level >30 IU dL⁻¹ [19], while others have recognized a target between 10 and 20 IU dL⁻¹ of FXIII activity [30]. For the UKHCDO, a monthly infusion of FXIII concentrate should be initiated from diagnosis and continued throughout pregnancy. FXIII levels should be monitored in order to keep the trough level >3 U dL [4]. Other authors have advocated for the use of 250 FXIII IU per week from the beginning of the pregnancy until the 6th month, followed by 500 IU per week and an additional dose of 1000 IU at the time of delivery [30,31]. In the French study previously mentioned, 11 pregnancies conducted under the administration of pdFXIII doses ranging from 400 to 800 IU per week throughout the pregnancy had a good outcome [21]; and increasing doses were prescribed during 3 pregnancies. These results suggest that at least one infusion of 400 IU per week of pdFXIII could lead to safe child birth [21].

In addition, the risk of bleeding during labor and delivery has also to be taken into account. Some authors have reported that 25% of post-partum hemorrhages occurred despite the administration of an additional dose before delivery [20]. However, Rugeri et al. have reported no bleeding complication during 5 vaginal deliveries and 6 cesarean sections, and the postpartum period offset by the administration of a single bolus of 1250 IU [21].

As for other RBDs, experts consider that the risk of epidural hematoma is increased in patients with a bleeding phenotype both at the time of insertion and at the time of removal of the epidural catheter, and that this type of anesthesia should therefore be avoided [3,4]. However, there is no recommendation regarding the use of epidural analgesia in women with severe FXIIIID who are administered concentrates. In the French series, no epidural analgesia was reported [21].

Conclusion and Future Remarks

To conclude, in addition to the life-threatening bleeding risk, the main issue faced by women with severe FXIIIID is the risk of miscarriage, which remain common. In rare cases, women are undiagnosed before pregnancy and experience repeated bleeding miscarriages which should prompt the investigation of a FXIIIID diagnosis, which can only be performed by determining FXIII activity. Although, women with severe FXIIIID can be diagnosed during childhood and can be under long-term prophylaxis, personalized care during pregnancy has to be initiated

as early as possible through collaborations between obstetricians and hematologists. The effectiveness of FXIII prophylaxis regarding the achievement of pregnancy leads to recommend monthly injections of at least 400 IU of FXIII as early as possible, but it is also reported that the administration of a single bolus, just before labor, is sufficient to prevent the specific bleeding related to the delivery and the postpartum period. The lack of data about the dosage of FXIII prophylaxis recommended throughout pregnancy should lead to future international prospective studies to investigate and propose treatment guidelines.

Conflicts of Interest

All authors read and approved the final manuscript. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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