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Title page

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Lucia Rugeri[1], Christophe Martinaud[2], Philippe Beurrier[3], Yvonne Borg[4], Hervé Chambost[5], Mirela Chirila-Hetsch[6], Dominique Desprez[7], Annie Harroche[8], Vanessa Milien[9], Brigitte Pan-Petesch[10], Sandrine Meunier[1]

Affiliations

1. Hospices Civils de Lyon, Unité Hémostase Clinique, Hôpital Louis Pradel, Hospices Civils de Lyon, Bron, France
2. Department of Medical Biology, Military Medical Center Percy, Clamart, France
3. Centre de Traitement de l'Hémophilie, CHU Angers, Angers, France
4. Unité Hémostase et Centre Régional de Traitement des maladies Hémorragiques, Institut de Biologie Clinique, Hôpital Charles Nicolle, Rouen, France
5. Centre for Bleeding Disorders, Pediatric Haematology Oncology Department, University Hospital La Timone, AP-HM, and Aix Marseille Univ, INSERM, INRA, C2VN, Marseille, France
6. Service d'Hématologie, Hôpital de Valence, Valence, France
7. Centre de Traitement de l'Hémophilie, CHU Strasbourg, Strasbourg, France
8. Hemophilia care centre, Hematology unit, Hôpital Universitaire Necker enfants malades, Paris, France
9. FranceCoag, University Hospital La Timone, AP-HM, Marseille, France
10. Unité Hémostase Service hématologie, CHU Brest, Brest, France

Corresponding author

Lucia Rugeri
Hospices Civils de Lyon
Unité Hémostase Clinique
Hôpital Cardiologique
59 Boulevard Pinel
69677 Bron Cedex
France
Tel. +33 4 72 11 88 10
lucia.rugeri@chu-lyon.fr

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Conflicts of Interest

All authors declare no conflicts of interest.

Abstract

Introduction: Congenital factor XIII deficiency is a very rare bleeding disorder affecting 33 patients in France. Besides its role in fibrin clot stabilization, factor XIII is involved in placental attachment. Fetal miscarriages represent a frequent and concerning issue for these patients. The aim of the present study was to describe clinical characteristics of women presenting severe congenital FXIII deficiency in France, to focus on gynecological and obstetrical events, and to report the management of these rare situations.

Methods: We conducted a retrospective study in the French Hemophilia Comprehensive Care and Clinical Hemostasis Centers. Women between 15 and 65 years with factor XIII activity <10 IU dL^{-1} were included. Biological, clinical and therapeutic events that occurred to these patients during their gynecological and obstetrical period were recorded. **Results:** Among 31 centers, eleven patients were included. The median age at diagnosis was 1.5 years (range: 0-35), and at inclusion it was 30 years (range: 15-63). Fetal miscarriage was the primary manifestations in 2 (18%) patients, the remaining were diagnosed during hemorrhage. Menorrhagias were reported by 2 women (27%), 13 pregnancies were reported by 9 women including one abortion. Every pregnancy was conducted under factor XIII substitution, no hemorrhagic episode was reported. Four patients (36%) experienced at least one fetal miscarriage with a total amount of 30 miscarriages with 6 occurring during substitution. **Conclusion:** Altogether, our data confirmed the high incidence of miscarriage in women with factor XIII deficiency. Good outcome of pregnancies required prophylaxis in accordance with international guidelines.

Introduction

Congenital factor XIII (FXIII) deficiency is a very rare life-threatening autosomal recessive bleeding disorder. FXIII is a plasmatic protein circulating as a tetramer comprising two A-chains and two B-chains. After activation, FXIII increases the resistance of clots and possibly plays many other roles, notably in angiogenesis, placental attachment and it is essential for maintaining pregnancy (1,2). Two separate genes (*F13A1* and *F13B*) located on 2 different chromosomes are responsible of the production of FXIII (3).

The prevalence of FXIII deficiency varies around the world. One in every 1-2 million live births is affected, with higher prevalence in consanguineous families (4,5). In Europe, a register based on 13 centers identified 42 patients, corresponding to 7% of rare bleeding disorders (sRBD)(6) In France, among the 476 patients with rare bleeding disorders registered in the FranceCoag Network, 33 patients (6%) present a severe FXIII deficiency (< 10 IU dL^{-1}) (7). FXIII-A deficiency is the most severe form which leads to neonatal umbilical haemorrhage in 80% of cases, and spontaneous intracranial haemorrhage in 30% of cases (4,8). Factor XIII deficiencies can also be revealed by induced bleeding, delayed wound healing, and repeated miscarriages (9). The minimum FXIII activity level required to prevent major bleeding remains controversial in the absence of controlled prospective data (10–12).

During the reproductive period of life, menstruation and pregnancy are 2 circumstances in which women with severe FXIII deficiency may experience an increased risk of bleeding. Yet little data in the literature are available as to how to manage these situations in women affected by FXIII deficiency due to the rarity of the disease. Because FXIII deficiency leads to frequent abortion in pregnant women, the knowledge of the gynecological issues and/or obstetric complications in affected women could be helpful to propose prophylactic treatment during pregnancy. A recent review of the literature highlighted the high frequency of pregnancy loss in these women and that treatment by FXIII concentrates is required for pregnancy success (9).

In addition, Naderi *et al.* reported data from 17 cases in Iran (13), but these authors revealed the lack of consistent data in Western countries.

The aim of the present study was to describe clinical characteristics of women presenting severe congenital FXIII deficiency in France, to focus on gynecological and obstetrical events, and to report the management of these rare situations.

Materials

A retrospective study based on medical files of patients followed in one of the French Hemophilia Comprehensive Care and Clinical Hemostasis Centers was conducted. Inclusion criteria were: follow-up in one of these centers, age between 15 and 65 years, and to have provided informed consent. Laboratory assessment of FXIII deficiency was performed using the Berichrom® FXIII activity assay (Siemens Healthcare Diagnostics, Tarrytown, NY, US). Because the diagnostic accuracy of FXIII measurements remains uncertain, in the present study the limit of quantification of the method to assess the FXIII activity level varied from < 1 IU dL^{-1} or < 10 IU dL^{-1} according to the analyzer and the laboratory. Data on medical history including demographic characteristics, age, and circumstance of diagnosis, and prophylactic treatment were recorded. Gynecological and obstetrical events including abortions, pregnancies, and modalities of treatment during pregnancy and delivery were particularly investigated. The study was approved by the medical ethics committee of the National Reference Center in Lyon.

Results

Eleven women from 31 centers were included. The median age at diagnosis was 1.5 years (range: 0-35), and at inclusion it was 30 years (range: 15-63). Consanguinity was reported in 2 patients. Nine patients presented a FXIII-A deficiency, while genotype was unavailable in 2 patients. Eight patients had FXIII levels less than 1%, and 3 0 had < 10% of FXIII. In 7 patients,

umbilical cord or cerebral hemorrhage was the primary clinical manifestation. The 2 remaining patients were diagnosed following fetal miscarriage with massive bleedings (Table 1).

At inclusion, prophylactic regimen was reported in 9 women, it was based on plasma-derived FXIII concentrates (pdFXIII; Fibrogammin, CSL Behring, Germany) administered at a variable dose per infusion (range: 500-2500 IU) and frequency of infusion outside pregnancy (range: every 3-8 weeks).

Menorrhagia was reported in 2 patients receiving prophylaxis with pdFXIII (Table 2). These patients were also treated with tranexamic acid, and one received combined oral contraceptives, and iron supplementation. Three patients did not report menorrhagia in the absence of prophylaxis.

Nine women experienced pregnancies. One patient had an abortion and 1 patient presented 12 miscarriages but no full-term pregnancy. Twelve deliveries were reported in 7 women: 4 patients experienced pregnancies without miscarriages, 3 had both pregnancies and miscarriages. Two preterm deliveries occurred, at 26 and 33 gestational weeks, respectively due to incompetent cervix or to premature rupture of membrane (Table 2). In the particular case of patient 8, a premature delivery occurred in a context of incompetent cervix and disseminated intra-vascular coagulation with a fetal death due to prematurity. In this woman, the diagnosis of inherited FXIII deficiency was made after this first bleeding complication.

Among the 30 miscarriages reported in 4 patients: 97% occurred during the first trimester. Six miscarriages occurred despite prophylactic regimen; for 3 of these very early miscarriages occurred under pre-gestational prophylaxis (1 infusion every 2 months) (Table 3).

All full term-pregnancies (n =11) were observed in women with prophylactic regimen. The doses and the frequency of infusion varied among included patients. One infusion at least per month was administered; the frequency of infusion ranged from 1 every 2 weeks to 1 every 4 weeks. There was no intensification of treatment during 8 pregnancies in 5 women. In 2

pregnancies the same dose was infused more frequently (1/3 weeks to 1/2 weeks, then 1/10 days) and patient 5 received a higher frequency of infusion only during the second trimester (Table 4). FXIII measurements were not systematically performed, leading to a systematic prescription at the same regimen. Only 2 centers were able to collect these data: the median of FXIIII levels before an infusion was 17 IU dL^{-1} (range: 7-30).

There were 5 vaginal deliveries and 6 cesarean sections. A bolus of a least 1250 IU of pdFXIII was administered just before the delivery in all patients and was sufficient to prevent hemorrhagic complications during delivery and post-partum. No epidural analgesia was performed. All newborns were healthy and no neonatal haemorrhagic complication associated with the birth process was reported. No bleeding complication was observed in the patient who had an abortion under infusion pdFXIII prior to the procedure.

Discussion

The present report also found that the main feature of pregnancies in women with FXIII deficiency is the high risk of miscarriage; 30 miscarriages were reported in 4 patients, including 12 in one patient who did not receive FXIII substitution before or during pregnancies. Six miscarriages occurred despite a substitution: one patient experienced 3 miscarriages due to incompetent cervix but one patient experienced 3 miscarriages probably due to a too low dose of pdFXIII. In a recent review Sharief *et al*. estimated that in women with severe FXIII deficiency the risk of miscarriages occurs in 2 out of 3 pregnancies. Without FXIII substitution, the achievement of pregnancy with birth of a healthy infant was estimated to be 10%, the miscarriages occurring mainly during the 1st trimester (9). The role of FXIII is well-known in coagulation but also in the pregnancy achievement. But the role of FXIII in maintaining of pregnancy is not completely understood. Although, FXIII is not essential to become pregnant, it has been reported that FXIII knockout mice can initiate pregnancies but died prematurely due

to vaginal bleedings concomitant with massive placental hemorrhage. Embryos exhibit no abnormalities, suggesting a maternal origin to these miscarriages (14). Fibrin and fibronectin are 2 substrates of FXIII and are major components of the layer between zona compacta and zona spongiosa, also known as Nitabuch's layer, which constitutes the separating line at the time of delivery. Co-localization of FXIII, fibrin and fibronectin has been described in this layer: its activity would participate in the maintenance of the integrity of this layer. Moreover, Nitabuch's layer would be involved in immune tolerance and FXIII deficiency could disrupt this function and participate in fetal losses (1).

Eleven pregnancies conducted under prophylaxis had a good outcome. During the study period, there were no guidelines available with regard to substitution regimen during pregnancy and a large variation of doses and frequency were reported by each center. Herein, 9 pregnancies were conducted and the pdFXIII doses ranged from 400 to 800 UI/week throughout the pregnancy. Increased doses were reported in only 3 pregnancies. These results suggest that at least one infusion of 400 UI/week could lead up to healthy child birth. The level of substitution remains debated but a target between 10 and 20 IU dL^{-1} of FXIII activity is (11). The United Kingdom Doctor's Haemophilia Organisation, recommend a monthly injection from the diagnosis of pregnancy, with a FXIII level above 3 IU dL^{-1} (15). Some authors advocate for the use of 250 FXIII UI/week from the beginning of the pregnancy until the 6^{th} month, followed by 500 IU/week and an additional dose of 1000IU at the time of the delivery (16,17). Furthermore, herein the administration of an additional dose before delivery prevented post-partum hemorrhage that has been described in previous studies; these series reported more than 25% of post-partum hemorrhage in this population, which represents a 5-fold increased risk as compared to healthy population in France (18).

In addition, a quarter of women with FXIII deficiency (n=3) did not experience menorrhagia before introduction of prophylaxis and among women receiving prophylaxis, 2 patients

reported menorrhagia; no life-threatening peritoneal bleeding was observed. In the literature, however, a high rate of peritoneal bleeding by ruptured ovarian cyst and of menorrhagia (26 to 64%) were described in women without prophylaxis (9,19,20), The low rate of gynecological bleeding in the series reported herein could be explained by prophylaxis treatment received by the patients.

One of the limitations of this study is the lack of measurement of FXIII levels to guide the frequency of infusions. The observational nature and the absence of control group represent other potential limitations of the study. But this is the biggest series reporting obstetrical outcome in pregnant women with severe FXIII deficiency in Western countries.

Taken together, despite the small number of patients due to the rarity of this bleeding disorder, the results confirm the high prevalence of miscarriages and the effectiveness of FXIII prophylaxis to achievement of pregnancy. An injection per month of at least 400 UI of FXIII as soon as possible, personalized individual care through collaboration between obstetricians, hematologists should allow successful outcome of each pregnancy.

Author contributions: Lucia Rugeri, Christophe Martinaud and Sandrine Meunier performed the research, designed the research study, analysed the data and wrote the paper. Philippe Beurrier, Yvonne Borg, Hervé Chambost, Vanessa Milien, Mirela Chirila, Dominique Desprez, Annie Harroche , Brigitte Pan-Petesch performed the research and reviewed the manuscript. 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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Tables

Table 1: Demographic, clinical, and prophylaxis regimen in 11 women with FXIII deficiency.

Patient	Age at inclusion, years	Age at diagnosis, years	FXIII level, IU dL-1	First bleeding symptom	Prophylactic regimen (pdFXIII), IU/weeks
1	15	1	<10	central nervous system	1250/4
2	22	0	<10	umbilical cord	500/3
3	28	0	<1	umbilical cord	2500/4
4	33	3	<1	hematoma	1500/4
5	47	1	<1	central nervous system	1250/4
6	25	2	<1	umbilical cord	1250/4
7	26	0	<1	umbilical cord	2500/4
8	42	31	<10	fetal miscarriages	none
9	40	3	<1	hemarthrosis	1750/4
10	41	18	<1	fetal miscarriages	1250/8
11	63	35	<1	umbilical cord	none

Table 2: Gynecological and obstetrical events in 11 women with severe FXIII deficiency.

Patient	Menorrhagia	Pregnancies (n=43)	Fetal miscarriages (n= 30)	Deliveries (n=12)
1	no	0	0	0
2	yes	0	0	0
3	no	1	0	1
4	yes	1	0	1
5	no	1	0	1
6	no	1	0	abortion
7	no	2	0	2
8	no	7	4	3
9	no	7	6	1
10	no	11	8	3
11	no	12	12	0

Table 3: Fetal miscarriages (n=30) in the 4 patients concerned.

Patient	Number of fetal miscarriage	FM without prophylactic treatment, n (%)	FM under prophylactic treatment, n (%)	Curettage, n (%)	Hemorrhagic complications
8	4	3 (75)	1 (25)	2 (50)	Yes
9	6	2 (33)	4 (77)	6 (100)	No
10	8	7 (87)	1 (23)	6 (75)	Yes
11	12	12 (100)	0 (0)	8 (66)	No

Table 4: Data of prophylactic regimen during pregnancies and mode of deliveries (n=11) in 7 women.

Patient	pdFXIII (IU)/infusion	Frequency (infusion/weeks or days)			Mode of delivery
		First trimester	Second trimester	Third trimester	
3	2500	1/3w	1/2w		Vaginal
4	1750		1/4w		Cesarean section
5	1250	1/2w	1/3w	1/2w	Cesarean section
7	2500		1/4w		Vaginal
	2500		1/4w		Vaginal
	1250		1/3w		Cesarean section
8	1250	1/3w	1/2w	1/10d	Cesarean section
	1250		1/3w		Cesarean section
9	1750		1/2w		Cesarean section
10	1250		1/3w		Vaginal
	1250		1/3w		Vaginal

w: weeks, d: days.