Received: 2 January 2024 | Revised: 5 May 2024 | Accepted: 16 May 2024

https://doi.org/10.1016/j.rpth.2024.102462

ORIGINAL ARTICLE

Perioperative management and neuraxial analgesia in women with factor XI deficiency (<60 IU/dL): a French multicenter observational study of 314 pregnancies

C. Flaujac[1] | D. Faille[2] | C. Lavenu-Bombled[3] | N. Drillaud[4] | D. Lasne[5] | P. Billoir[6] | C. Desconclois[7] | L. Touzet[8] | A. Lebreton[9] | I. Diaz-Cau[10] | R. d'Oiron[11] | M. Giansily-Blaizot[10] | B. Wibaut[12] | P. Beurrier[13] | F. Volot[14] | L. Rugeri[15] | V. Roussel-Robert[16] | E. de Raucourt[17,18]

[1]Laboratoire de biologie médicale, Secteur hémostase, Centre hospitalier de Versailles (André Mignot), Le Chesnay-Rocquencourt, France

[2]Service d'hématologie biologique, Assistance Publique Hôpitaux de Paris, Centre-Université de Paris, hôpital Bichat, Paris, France

[3]Service d'hématologie biologique, Assistance Publique Hôpitaux de Paris, Hôpital Bicêtre, Université Paris-Saclay, Le Kremlin-Bicêtre, France

[4]Centre de Ressources et Compétences des Maladies Hémorragiques Constitutionnelles rares, Centre hospitalier Universitaire, Nantes, France

[5]Service d'hématologie biologique, Assistance Publique Hôpitaux de Paris, Centre-Université de Paris, Hôpital Necker Enfants Malades, Paris, France

[6]Service d'hématologie biologique, Centre hospitalier universitaire de Rouen, Rouen, France

[7]Service d'hématologie biologique, Assistance Publique Hôpitaux de Paris, Hôpital Antoine Béclère, Université Paris-Saclay, Clamart, France

[8]Laboratoire de biologie médicale, Centre hospitalier de Valencienne, Valencienne, France

[9]Service d'hématologie biologique, Centre hospitalier universitaire de Clermont Ferrand, Université Clermont Auvergne, Clermont-Ferrand, France

[10]Service d'hématologie biologique, Centre hospitalier universitaire de Montpellier, Montpellier, France

[11]Centre de Référence de l'Hémophilie et des Maladies Hémorragiques Constitutionnelles rares, Assistance Publique Hôpitaux de Paris, Hôpital Bicêtre, Université Paris-Saclay, Le Kremlin-Bicêtre, France

[12]Centre de Ressources et Compétences des Maladies Hémorragiques Constitutionnelles rares et Centre de Référence maladie de Willebrand, Centre hospitalier régional universitaire de Lille, Lille, France

[13]Centre de Ressources et Compétences des Maladies Hémorragiques Constitutionnelles rares, Centre hospitalier universitaire d'Angers, Angers, France

[14]Centre de Ressources et Compétences des Maladies Hémorragiques Constitutionnelles rares, Centre hospitalier universitaire de Dijon, Dijon, France

[15]Centre de Ressources et Compétences des Maladies Hémorragiques Constitutionnelles rares, Hospices Civils de Lyon, Lyon, France

[16]Centre de Ressources et de Compétences des Maladies Hémorragiques Constitutionnelles rares, Assistance Publique Hôpitaux de Paris, Centre-Université de Paris, Hôpital Cochin, Paris, France

[17]Centre de Ressources et Compétences des Maladies Hémorragiques Constitutionnelles rares, centre hospitalier de Versailles (André Mignot), Le Chesnay, France

[18]Service d'hématologie biologique, Assistance Publique Hôpitaux de Paris, Nord Université de Paris Centre, Hôpital Beaujon, Clichy, France

Correspondence
Claire Flaujac, Laboratoire de biologie médicale, Secteur hémostase, Centre hospitalier de Versailles (André Mignot), 78150 Le Chesnay-Rocquencourt, France.
Email: cflaujac@ght78sud.fr

Handling Editor: Michael Makris

Abstract

Background: Factor (F)XI deficiency is a rare bleeding disorder with a poor correlation between bleeding tendency and FXI level. Management of pregnant women with FXI deficiency is not clearly established, especially regarding neuraxial analgesia (NA).

Objectives: A retrospective multicenter observational study was conducted in French hemostasis centers on pregnant women with FXI of <60 IU/dL.

Methods: Data to report were (i) FXI levels before pregnancy and at time of delivery, (ii) type of NA and delivery management modalities, and (iii) possible complications related to NA and bleeding complications.

Results: Three hundred fourteen pregnancies in patients with FXI deficiency of <60 IU/dL were reported (from 20 centers); among them, 199 NA procedures have been completed (137 epidurals and 61 spinals, 1 had both). The period of childbirth was mostly from 2014 to 2020 (281/314; 89.5%). Congenital FXI deficiency was established with certainty by investigators in 32.8% patients (*n* = 103). Previous bleedings were described in 20.4% of the patients (64/314; 45.3% cutaneous, 31.3% gynecologic, and 15.6% postsurgical). Thirteen deliveries had an NA procedure with FXI of <30 IU/dL, 42 with FXI of 30-40 IU/dL, and 118 with FXI of 40-60 IU/dL. Median FXI levels at delivery in the epidural and spinal groups were not significantly different but were significantly lower in the group without NA by medical staff contraindications. There were no complications related to NA. A 17.5% postpartum hemorrhage or excessive postpartum bleeding incidence was reported, which is consistent with previous data.

Conclusion: Our data support the use of a 30 IU/dL FXI threshold for NA, as suggested by the French proposals published in August 2023.

KEYWORDS
bleeding, epidural anesthesia, factor XI, observational study, spinal anesthesia

Essentials

- Factor (F)XI deficiency is a rare bleeding disorder with a poor correlation between bleeding tendency and FXI level. The management of FXI deficiency in pregnant women is not yet established, particularly with regard to neuraxial analgesia (NA).
- We conducted an anonymous retrospective study from 2009 to 2020 of women with FXI activity level below 60 IU/dL before pregnancy and/or below 60 IU/dL at time of delivery in 20 French centers. Of the 314 reported pregnancies, 199 NA procedures were completed (137 epidurals and 61 spinals, 1 had both). There were no complications related to NA, and 173 NAs were allowed with known FXI levels at time of delivery ranging from 17 to 60 IU/dL with a mean FXI level at time of delivery of 44.2 ± 9.5 IU/dL.
- Our results support the use of a 30 IU/dL threshold for NA (all types of NA in women with no bleeding history: spinal and epidural) at time of procedure or for catheter removal. However, we also reported a 17.5% incidence of postpartum hemorrhage or excessive postpartum bleeding, which is in accordance with previous studies. Our results now need to be confirmed by large prospective studies.

1 | INTRODUCTION

Constitutional factor (F)XI deficiency is a rare bleeding disorder caused by mutations in the F11 gene [1] and was first described in the medical literature in 1953 [2]. In the general population, the prevalence of biallelic forms (homozygous or compound heterozygous) is estimated to be between 1 and 10 per 1 million. In these cases, FXI level will be lower than 20 IU/dL. In heterozygous patients, FXI levels are expected to be between 20 IU/dL and 60 IU/dL. The incidence of FXI deficiency (heterozygous) is higher in individuals of Ashkenazi Jewish descent, where it is estimated to affect 8% of the population [3–5]. In most cases, the bleeding tendency in individuals with FXI deficiency, even with very low factor levels, is mild. Affected individuals may experience mucocutaneous bleeding episodes (menorrhagia, especially in women) following trauma or surgery, including dental procedures, tonsillectomies, or surgery involving the urinary or genital tracts [3–5]. Most often, the bleeding severity of the disorder does not correlate with FXI activity levels, so the management of these patients remains a challenge between bleeding risk and the potential risks of replacement therapy with FXI concentrate or fresh frozen plasma (FFP).

During pregnancy, procoagulant factors and inhibitors of coagulation vary in different ways. Some factors decrease, such as protein S, while others increase, such as fibrinogen, FVII, FVIII and von Willebrand factor. Some factors remain stable, and the behavior of FXI is unclear [6,7]. Normal FXI activity ranges between 60 and 150 IU/dL in a healthy parturient in the third trimester. Management of FXI deficiency in pregnant women is not established yet, especially regarding neuraxial analgesia (NA). In 2018, the CoMETH group (Coordination médicale pour l'étude et le traitement des maladies hémorragiques constitutionnelles), which is a French working group on hemostasis part of the French Society of Haematology, conducted a national

survey among French physicians (32 centers) to evaluate the FXI threshold used to allow NA. This survey showed highly heterogeneous practices, with FXI levels ranging from 30 to 60 IU/dL and most centers (16/36) using a threshold of 40 IU/dL [8].

We report, in this paper, a retrospective multicenter observational study on a large French cohort of women with FXI deficiency (FXI activity level below 60 IU/dL) who underwent childbirth with the aim to assess FXI levels used to achieve NA in real-life practice and to expand data on the safety of NA in women with FXI deficiency during labor, possible complications related to NA, and bleeding complications.

2 | METHODS

2.1 | Study population and data collection

This was an anonymous retrospective chart review, which was approved by the institutional medical ethics committee of the Centre Hospitalier de Versailles in accordance with the Declaration of Helsinki and the Institut National des Données de Santé. Each center evaluated electronic medical records to include women with FXI activity levels below 60 IU/dL before pregnancy and/or below 60 IU/dL at time of delivery. Women were informed of their enrolment in the study and were able to leave the study. The retrospective study extends from 2009 to 2020. Health-related data included laboratory data on hematological parameters and clinical data. Laboratory data included FXI activity levels and, if possible, activated partial prothrombin time (aPTT) ratio before pregnancy and at time of delivery. As it was an anonymous chart review, birth date was not reported, but the year of birth of the women and the age at time of pregnancy were recorded. The notion of congenital deficiency was evaluated by the investigators, and if this was the case, the possibility of having had a molecular characterization of the FXI deficiency and/or a family investigation was recorded.

Clinical data included mode of delivery (planned vaginal delivery, planned cesarean section, unplanned vaginal delivery, triggered vaginal delivery, or emergency cesarean section). Type of anesthesia (spinal or epidural), bleeding complications of anesthesia or delivery, and, if possible, estimated blood loss, administration of hemostatic treatments (tranexamic acid, FFP, FXI concentrate [with a plasma-derived, purified, and virally inactivated FXI concentrate used in France], and red blood cell transfusion), as well as data on the personal and familial history of bleeding were collected.

Postpartum hemorrhage (PPH) was an item indicated by investigators in each case (yes or no). Concerning evaluation of excessive bleeding at time of delivery, if blood losses were clearly mentioned (in mL), PPH could be evaluated. PPH was retained if bleeding was >500 mL in accordance with the French Gynaecologists guideline, which classifies PPHs into categories of minor (500-1000 mL blood loss) and major (>1000 mL blood loss) [9]. If PPH was reported by the investigators with no blood loss, these cases were classified as “excessive bleeding” but not as PPH.

2.2 | Statistical analysis

Categorical variables are presented as counts with percentages. FXI levels reported as <1 IU/dL, <5 IU/dL, or <10 IU/dL by investigators were assigned as 1 IU/mL, 5 IU/ mL, or 10 IU/mL, respectively, in order to include this measurement in the calculations of means and medians. Continuous variables are presented as means with SDs or medians with ranges. Continuous variable values were compared using the paired *t*-test or Mann–Whitey U-test. Statistical analyses were

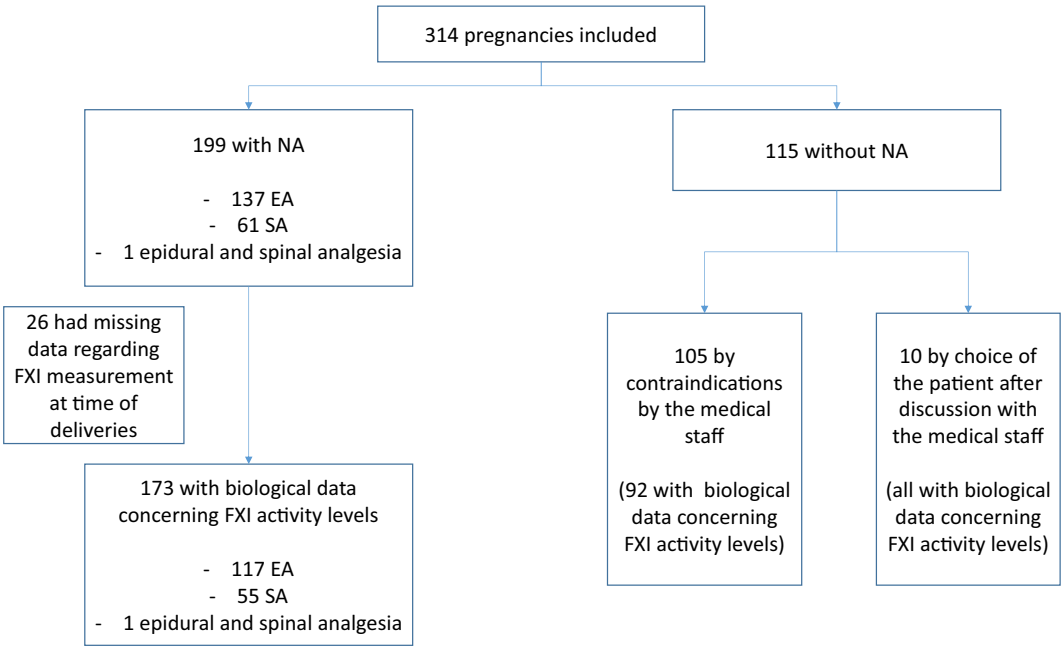

FIGURE 1 Flow chart of the study. EA, epidural analgesia; FXI, factor XI; NA, neuraxial analgesia; SA, spinal analgesia.

performed using Statistique R software BiostaTGV website (INSERM Medecine Sorbonne University).

3 | RESULTS

Overall, 314 pregnancies were reported in 20 hemostasis centers. The flow chart of the study is presented in Figure 1. Concerning NA, 199 (63 %) have been completed (137 epidurals [42.3%] and 61 spinals [18.8%]; 1 had combined spinal and epidural). One hundred fifteen pregnancies did not have NA (37%), 10 by choice of the patient after discussion with the medical staff and 105 by contraindications by the medical staff. As indicated in Table 1, the period of delivery was mostly 2014-2020 (89.5%) and age at delivery was between 20 and 30 years (46.5%) and 30 to 40 years (47.8%). Congenital FXI deficiency was established with certainty by investigators in 32.8% patients (n = 103), and 27/103 were genotyped. Anti-FXI antibodies were not reported by investigators. Overall, prior to this study, a personal bleeding phenotype was reported by 20.4% patients (64/314; cutaneous oropharyngeal cavity bleeding 45.3% [29/64], gynecologic bleeding 31.3% [20/64], and postsurgery bleeding 15.6% [10/64]). In addition, 24 pregnancies (7.42%) had a positive familial bleeding history.

TABLE 1 Demographic data and clinical characteristics of patients.

Clinical characteristics, N = 314	n (%)
Period of delivery	
2009-2013	33 (10.5)
2014-2020	281 (89.49)
Age at term of delivery, (y)	
<20	9 (2.87)
20-30	146 (46.5)
30-40	150 (47.77)
>40	9 (2.87)
Bleeding phenotype prior to this study	
None	227 (72.3)
Yes	64 (20.4)
After surgery	10 (15.6)
Cutaneous and oral cavity bleeding	29 (45.3)
Gynecologic bleeding	20 (31.3)
Others	5 (7.8)
Missing information	23 (6.37)
Personal and familial history	
Congenital phenotype	103 (32.8)
Molecular characterization	27 (8.33)
Noncongenital deficiency	16 (5.10)
Unknown congenital deficiency or missing information	195 (62.10)
Positive bleeding familial history	24 (7.42)
NA	
None, by choice of the patient	10 (3.18)
None by contraindications	105 (33.44)
Spinal analgesia	61 (18.82)
Epidural analgesia	137 (42.28)
Spinal and epidural analgesia	1 (0.30)

NA, neuraxial analgesia.

In the NA group, 173 of the 199 pregnancies (117, epidural analgesia; 55, spinal analgesia; and 1 had both) completed the study with all biological data concerning FXI activity levels. As indicated in Table 2, median FXI activity levels at delivery in the epidural and spinal groups were not significantly different (P = .204) nor the aPTT ratio (data not shown). However, the FXI activity levels were significantly lower in the group "pregnancies with contraindications to NA by the medical staff" (median, 27.5; 1-54 IU/dL; P < .0005). Contraindication of NA was reported in 105 deliveries in which 22 patients had FXI level of <30 IU/dL, among them 12 were below 5 IU/dL, and in 8 cases, FXI concentrates were administered for delivery management.

Among the 173 pregnancies with FXI levels reported at time of delivery, 13 deliveries had an NA with FXI activity level below 30 IU/dL ranging from 17 to 29 IU/dL. One of them had a severe FXI deficiency (<1 IU/dL) and received a FXI infusion (20 IU/kg) for an emergency cesarean section with a FXI level at time of delivery of 21 IU/dL. Forty-two deliveries had NA with FXI activity levels in 30 to 39 IU/dL range, and 63 deliveries had NA with FXI activity levels in 40 to 49 IU/dL range (45 epidurals, 17 spinals, and 1 epidural and spinal analgesia). Fifty-five deliveries had FXI activity levels in 50 to 60 IU/dL range. Overall, 118 NAs were realized below 50 IU/dL (range, 17-49 IU/dL). All data are presented in Figure 2. Missing FXI levels at time of delivery were observed in 26 deliveries; among them, only 3 women had severe congenital FXI deficiency with FXI levels of ≤2 IU/dL. Two women with spinal anesthesia received FXI concentrate (26 IU/kg for one, dose not reported for the second), suggesting that FXI levels were probably above 20 IU/dL at time of NA. One woman had an unknown congenital FXI deficiency at 2 IU/dL at time of delivery and got spinal analgesia. In the other 23 women with unknown FXI levels at time of delivery, FXI levels prior to pregnancy ranged from 30 to 59 IU/dL. Thus, we can speculate that no additional women had NA with FXI level of <30 IU/dL at time of delivery. No substitutive treatment with FFP or FXI concentrate was given prior to delivery among women with FXI levels above 30 IU/dL. Overall, 11 women received FXI infusion (3 in NA group and 8 in the group "contraindication of NA"). It should be noted that 2 patients had tranexamic acid before delivery. However, the delay in relation to the realization of the NA is not known. There were no complications related to NA (during the procedure or catheter removal).

Overall, 17.5% (55/314) of PPH or excessive bleeding were reported by investigators. With the information mentioned by the investigators in 36 pregnancies, blood losses were clearly mentioned as >500 mL and classified as PPH. In 19 deliveries, the blood loss

TABLE 2 Factor XI activity level at delivery and mode of delivery in different groups of pregnant women.

Type of NA	Spinal analgesia (*n* = 62)	Epidural analgesia (*n* = 138)	Without NA by medical contraindications (*n* = 105)	Without NA by choice of the woman (*n* = 10)
FXI activity level at delivery (IU/dL)	(*n* = 56)	(*n* = 118)	(*n* = 92)	(*n* = 10)
Mean ± SD	43.1 ± 11.2	44.7 ± 8.5	26.8 ± 13.9	38 ± 6.72
Median (range)	46 (17-65)	46.5 (22-60)	27.5 (1-54)	38.5 (27-47)
Mode of delivery (*n*):				
Planned vaginal delivery (*n* = 30)	*n* = 1 (1.6%)	*n* = 22 (15.9%)	*n* = 7 (6.6%)	*n* = 0
Planned cesarean section (*n* = 47)	*n* = 35 (56.4%)	*n* = 3 (2.2%)	*n* = 9 (8.5%)	*n* = 0
Unplanned vaginal delivery (*n* = 177)	*n* = 3 (4.8%)	*n* = 85 (61.6%)	*n* = 79 (75.2%)	*n* = 10 (100%)
Triggered vaginal delivery (*n* = 6)	*n* = 0	*n* = 5 (3.6%)	*n* = 1 (0.9%)	*n* = 0
Emergency cesarean section (*n* = 55)	*n* = 23 (37%)	*n* = 23 (16.7%)	*n* = 10 (9.5%)	*n* = 0

FXI, factor XI; NA, neuraxial analgesia.

information was missing, but PPH was reported most of the time because tranexamic acid, uterotonics injection, and/or manual extraction of retained placenta were used; these cases were classified as excessive blood losses. Overall, PPH or excessive *postpartum* bleeding could be attributed in 30/55 deliveries to various gynecologic causes, mainly to uterine atony, but in 25/55 deliveries, the cause was unknown or not mentioned by the investigators. Twenty-one pregnancies were reported with a FXI at term of birth <20 IU/dL, and 11/21 (52.3%) had a personal bleeding history prior to delivery. Only 1 PPH was reported (700 mL) in women with severe FXI deficiency (<20 IU/dL) and in women with a FXI level below 5 IU/dL at time of delivery, despite FXI infusion prior to vaginal delivery. Overall, acid tranexamic was reported as a treatment of PPH or excessive bleeding at least 16 times by investigators, FFP 11 times, and blood transfusion 10 times. In women who experienced cesarean section (planned cesarean section [*n* = 47] or emergency cesarean section [*n* = 55]), PPH was reported 29/102 (28.4%), 16 times as a confirmed PPH with a mean blood loss of 1.5 L and 8 times classified as excessive *postpartum* bleeding. In this observational study, PPH was not the first endpoint, and some data could be missing; tranexamic acid treatment in PPH is only reported in 8 cases and FFP in 3 cases in the management of PPH in addition to gynecologic care and blood transfusion (*n* = 4) if needed. No thrombosis has been reported by investigators.

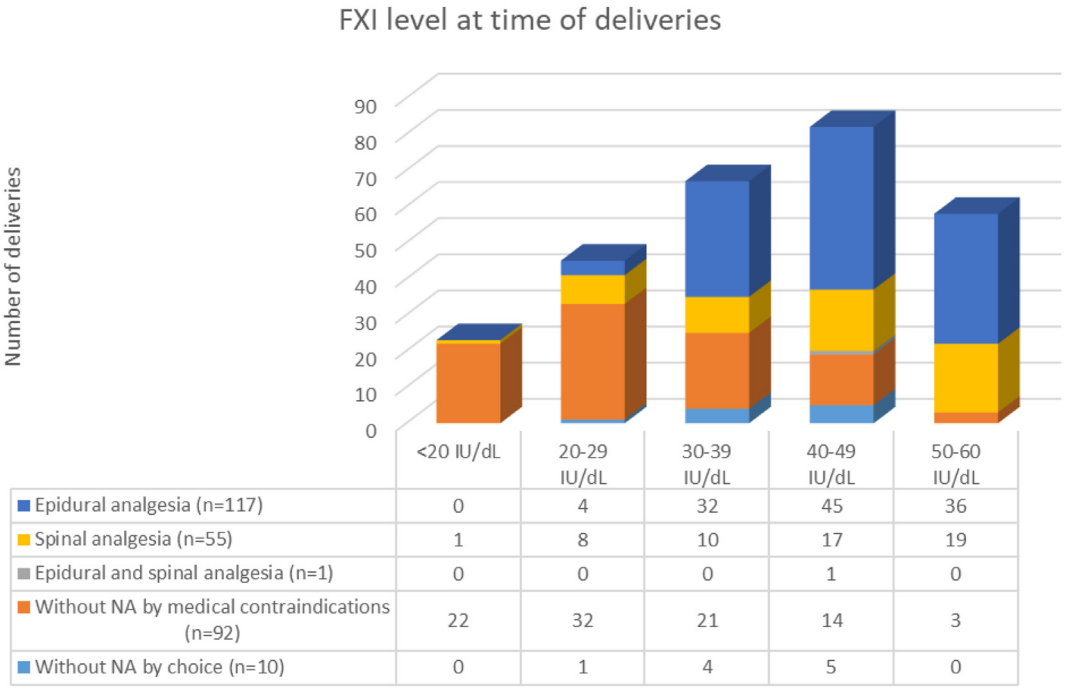

FIGURE 2 Factor (F)XI level at time of deliveries in each group. NA, neuraxial analgesia.

4 | DISCUSSION

Seligsohn [10] reported that heterozygote patients may have a slightly prolonged aPTT or values within the normal range. Moreover, during pregnancies, the aPTT usually shortens due to the increase in FVIII, so aPTT could be insufficient to assess hemostatic balance in FXI-deficient women. FXI level is still the main parameter used by anesthesiologists in order to allow NA because global hemostasis tests such as thrombin generation are not easy to perform in all laboratories and have a lack of standardization [11]. Nevertheless, management of women with FXI deficiency during labor is challenging, especially concerning NA. In 2021, Peterson et al. [12] reviewed the outcomes of 2047 neuraxial anesthetics in patients with hemorrhagic disorders/tendencies and underlined the paucity of the literature. Concerning FXI, they mentioned 11 studies relating to NA in patients with FXI deficiency, including 4 case reports/case series and 4 retrospective cohort studies. Overall, they mentioned 66 neuraxial procedures performed, all in women for labor analgesia, with 4 combined spinal epidurals and 1 spinal procedure. NA was placed at FXI levels ranging from 5 to 74 IU/dL. No FXI values were reported at the time of catheter removal. There were no epidural or spinal hematomas. A recent retrospective case-control study with patients with FXI ranging from 20 to 70 IU/dL reported 51 NAs with no observed complications. In this study, only 3 patients received prophylaxis with FFP, one of whom also received antifibrinolytic therapy [13]. A more recent retrospective monocentric observational study reported 206 deliveries in women with FXI levels below 70 IU/dL; 168 of them had NA, but only 97 had FXI levels under 50 IU/dL, and only 16 between 31 and 40 IU/dL [7]. No study reported any bleeding complications related to NA. In 2018, the CoMETH group conducted a national survey among French physicians (32 centers) showing heterogeneous practices in France regarding the FXI threshold that physicians answered to allow NA, ranging from 30 to 60 IU/dL. This real-life large observational multicenter study confirmed this heterogeneity as 173 NAs were allowed with known FXI levels at time of delivery ranging from 17 to 60 IU/dL with a mean FXI level at time of delivery of 44.2 ± 9.5 IU/dL and only 13 patients with FXI level under 30 IU/dL This is in accordance with the results of the previous national survey which showed that NA was avoided under this FXI level.

Among the 199 women who underwent NA, 3 received substitutive treatment, thus representing only 1.5% of the cohort. Whereas in the group with contraindication of NA, there were 22 patients with FXI of <30 IU/dL, among them 12 were below 5 IU/dL, and in 8 cases, FXI concentrates were administered for delivery management. Our study is the largest, including 199 NAs during 314 deliveries in women with FXI under 60 IU/dL. Thirteen deliveries had FXI activity levels under 30 IU/dL in range of 17 to 29 IU/dL, 42 in 30 to 39 IU/dL range, and 63 in 40 to 49 IU/dL range. It should be noted that of the 26 NAs performed with an unknown FXI level at the time of delivery, 1 was performed in a woman with severe congenital FXI deficiency (FXI level of 2 IU/dL). Otherwise, regarding FXI levels reported before pregnancy, we can speculate that all other women who underwent NA had FXI levels at least above 20 to 30 IU/dL at time of delivery. In total, no bleeding complication related to NA was reported among these 199 cases.

There is no consensus on the safe level of FXI necessary for neuraxial anesthesia in women with FXI deficiency. Two publications proposed recommendations for delivery management and NA in FXI-deficient women. These recommendations were formulated from observational data [14,15] and expert opinion [15]. Concerning NA, for Katz et al. [14], bleeding history was more important than factor concentrations because factor concentrations do not predict bleeding. In the guidelines of the Royal College of Obstetricians and Gynaecologist, central NA should not be given to women with low FXI levels with a known bleeding phenotype, where the phenotype is not clear, or when there is a severe reduction in level [15]. In those with a nonbleeding phenotype, discussion and counseling should be given regarding the risks and benefits of allowing NA with or without factor replacement [15]. Recently, the French proposal for management of rare bleeding disorders suggests a hemostatic FXI level of 30 IU/dL to allow NA in women with no personal history of bleeding complications [16]. Our results support the use of a 30 IU/dL threshold for NA (all types of NA in women with no bleeding history: spinal and epidural) at time of procedure or for catheter removal.

Concerning the PPH evaluation, there is a bias in our study as blood loss evaluation was not systematically recorded. The definition of PPH is not unique. In fact, PPH is mostly defined as blood loss of >500 mL after vaginal delivery or of >1000 mL after cesarean delivery [17]. The American College of Obstetricians and Gynaecologists formerly used this definition but has updated their most recent PPH Practice Bulletin to define PPH as either cumulative blood loss of >1000 mL or blood loss accompanied by the signs and symptoms of hypovolemia, regardless of delivery route [18]. The Royal College of Obstetricians and Gynaecologists [19] and the French guidelines [9] classify PPHs into categories of minor (500-1000 mL blood loss) and major (>1000 mL blood loss). Thirty-six pregnancies (36/314; 11.5%) were evaluated as mentioned by guidelines and clearly indicated by investigators (>500 mL or >1000 mL) over the 55 classified as PPH by investigators (55/314; 17.5%). PPH has been reported in women with mild and severe FXI deficiency, leading to a debate regarding the need for replacement therapy before delivery. Despite bias described previously in our study, PPH or excessive postpartum bleeding evaluated at 17.5% is clearly in accordance with previous studies where PPH data were reported at 17% in 490 pregnancies (250 women), 11% in 206 pregnancies, and 18% in 372 pregnancies [6,7,20]. PPH is also reported in a specific group with a more frequent PPH in women with FXI ranging from 20 to 70 IU/dL during cesarean deliveries (odds ratio, 2.73; 95% CI, 1.02-7.26; P =.04) [13]. Thus, early replacement therapy using FFP or FXI concentrate is probably appropriate for women with severe FXI defects in case of cesarean.

This large retrospective multicenter study showed that NA is safe in women with no personal bleeding history and with FXI deficiency ranging from 30 to 60 IU/dL; this has to be confirmed by large prospective studies.

ACKNOWLEDGMENTS

The authors thank all of the participants that provided cases for inclusion in this study: Dr A. Cassini (Division of Angiology and Hemostasis, University Hospitals of Geneva, Switzerland), Dr C. Cavalie (Service d'hématologie biologique, Assistance Publique Hôpitaux de Paris, Centre-Université de Paris, Hôpital Bichat, Paris, France), Dr B. Guillet (Centre de Ressources et Compétences des Maladies Hémorragiques Constitutionnelles rares [CRC-MHC], Centre Hospitalier Universitaire de Rennes, France), Dr D. Desprez (CRC-MHC, Centre Hospitalier Universitaire de [CHU] Strasbourg, France), Dr S. Combe (CRC-MHC, Centre Hospitalier Universitaire Cochin, Paris, France), Dr M. Fretigny (CRC-MHC, Hospices Civils de Lyon, France, France), Dr B. Pan Petesch (CRC-MHC, CHU Brest, France), Dr C. Poumayou (CRC-MHC Assictance Publique Hôpitaux de Marseille, France), Dr S. Timsit (CRC-MHC, Centre Hospitalier Universitaire Necker-Enfants malades, Paris, France), Dr M. Trossaert (CRC-MHC, CHU Nantes, France), and Dr A. Ramassamy (CRC-MHC, CHU Poitiers, France).

FUNDING

The FXI Study has been performed with the support of the CoMETH group (Coordination médicale pour l'étude et le traitement des maladies hémorragiques) and the SFTF (Société Française de Thrombose et d'Hémostase).

AUTHOR CONTRIBUTIONS

C.F., R.d.O., M.G.B., B.W., P.B., F.V., L.R., V.R.R., and E.d.R. designed the study; C.F., D.F., C.L.B., N.D., D.L., P.B., C.D., L.T., A.L., I.D.C., R.d.O., M.G.B., B.W., P.B., F.V., L.R., V.R.R., E.d.R., B.G., D.D., S.C., M.F., B.P.P., C.P., S.T., M.T., and A.R. collected data; C.F. and E.d.R. analyzed and interpreted data, performed statistical analysis, and wrote the manuscript. All coauthors were given the opportunity to revise and comment on the text and content of manuscript.

RELATIONSHIP DISCLOSURE

Authors and collaborators have no disclosure and no conflict of interest with respect to the results contained in this manuscript or the redaction of this manuscript.

Declaration of AI and AI-Assisted Technologies in the Writing Process

No AI or AI-assisted technologies were used in the writing process of this manuscript.

ORCID

C. Flaujac https://orcid.org/0000-0002-3662-3416

X

C. Flaujac @ClaireFlaujac

REFERENCES

[1] Asakai R, Davie EW, Chung DW. Organization of the gene for human factor XI. *Biochemistry*. 1987;26:7221–8.

[2] Rosenthal RL, Dreskin OH, Rosenthal N. New hemophilia-like disease caused by deficiency of a third plasma thromboplastin factor. *Proc Soc Exp Biol Med Soc Exp Biol Med*. 1953;82:171–4.

[3] Bolton-Maggs PHB. Factor XI deficiency—resolving the enigma? *Hematology Am Soc Hematol Educ Program*. 2009:97–105.

[4] James P, Salomon O, Mikovic D, Peyvandi F. Rare bleeding disorders - bleeding assessment tools, laboratory aspects and phenotype and therapy of FXI deficiency. *Haemophilia*. 2014;20:71–5.

[5] Mumford AD, Ackroyd S, Alikhan R, Bowles L, Chowdary P, Grainger J, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2014;167:304–26.

[6] Davies J, Kadir R. The management of factor XI deficiency in pregnancy. *Semin Thromb Hemost*. 2016:732–40.

[7] Handa S, Sterpi M, Sacchi De Camargo Correia G, Frankel DS, Beilin Y, Cytryn L, et al. Obstetric and perioperative management of patients with factor XI deficiency: a retrospective observational study. *Blood Adv*. 2023;7:1967–75.

[8] Abstracts. *Haemophilia*. 2020;26:3–40.

[9] Goffinet F, Mercier F, Teyssier V, Pierre F, Dreyfus M, Mignon A, et al. [Postpartum haemorrhage: recommendations for clinical practice by the CNGOF (December 2004)]. *Gynecol Obstet Fertil*. 2005;33:268–74.

[10] Seligsohn U. Factor XI deficiency in humans. *J Thromb Haemost*. 2009;7:84–7.

[11] Kasonga F, Feugray G, Chamouni P, Barbay V, Fresel M, Chretien MH, et al. Evaluation of thrombin generation assay in factor XI deficiency. *Clin Chim Acta*. 2021;523:348–54.

[12] Peterson W, Tse B, Martin R, Fralick M, Sholzberg M. Evaluating hemostatic thresholds for neuraxial anesthesia in adults with hemorrhagic disorders and tendencies: a scoping review. *Res Pract Thromb Haemost*. 2021;5:e12491. https://doi.org/10.1002/rth2.12491

[13] Stoeckle JH, Bogue T, Zwicker JI. Postpartum haemorrhage in women with mild factor XI deficiency. *Haemophilia*. 2020;26:663–6.

[14] Katz D, Beilin Y. Disorders of coagulation in pregnancy. *Br J Anaesth*. 2015;115:ii75–88.

[15] Pavord S, Rayment R, Madan B, Cumming T, Lester W, Chalmers E, Myers B, Maybury H, Tower C, Kadir R, on behalf of the Royal College of Obstetricians and Gynaecologists. Management of inherited bleeding disorders in pregnancy. *BJOG*. 2017;124:e193–263. https://doi.org/10.1111/1471-0528.14592

[16] Trossaert M, Chamouard V, Biron-Andreani C, Casini A, De Mazancourt P, De Raucourt E, et al. Management of rare inherited bleeding disorders: proposals of the French Reference Centre on Haemophilia and Rare Coagulation Disorders. *Eur J Haematol*. 2023;110:584–601.

[17] Dahlke JD, Mendez-Figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *Am J Obstet Gynecol*. 2015;213:76.e1–10. https://doi.org/10.1016/j.ajog.2015.02.023

[18] Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 183: postpartum hemorrhage. *Obstet Gynecol*. 2017;130:e168–86. https://doi.org/10.1097/AOG.0000000000002351

[19] Mavrides E, Allard S, Chandraharan E, Collins P, Green L, Hunt BJ, Riris S, Thomson AJ, on behalfof the Royal College of Obstetricians and Gynaecologists. Prevention and management of postpartum haemorrhage. *BJOG*. 2016;124:e106–49. https://doi.org/10.1111/1471-0528.14178

[20] Wiewel-Verschueren S, Arendz IJ, Knol H M, Meijer K. Gynaecological and obstetrical bleeding in women with factor XI deficiency – a systematic review. *Haemophilia*. 2016;22:188–95.