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ORIGINAL ARTICLE

Reproductive health and hemostatic issues in women and girls with congenital factor VII deficiency: A systematic review

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Abstract

Background: Congenital factor VII (FVII) deficiency is an inherited bleeding disorder, with heterogenous bleeding symptoms. Women with FVII deficiency face hemostatic challenges during menstruation, ovulation, and childbirth. This systematic review evaluated prevalence and management of bleeding symptoms associated with gynecological and obstetric issues in women with FVII deficiency.

Methods: Databases (BIOSIS Previews, Current Contents Search, Embase, and MEDLINE) were searched for studies reporting FVII deficiency and gynecological or obstetric issues in women. Articles were screened using Joanna Briggs Institute checklists and relevant data extracted.

Results: One hundred fourteen women were identified from 62 publications. Forty-six women had severe deficiency (FVII:C < 5% or <5 IU/dl). Heavy menstrual bleeding (HMB) was the most common bleeding symptom ($n = 94$; 82%); hospitalization and urgent medical/surgical interventions for acute HMB episodes were required in 16 women (14%). Seven women reported ovarian bleeding (6%); other bleeding symptoms varied. Patient management was inconsistent and included hemostatic and hormonal treatments. Only four women (7%) reporting vaginal bleeding during pregnancy. Postpartum hemorrhage (PPH) occurred following 12/45 deliveries (27%; 5 [42%] requiring blood transfusion) and was not necessarily prevented by prophylaxis (8 women).

Conclusion: Women with congenital FVII deficiency have an increased risk of HMB, ovarian bleeding, and PPH, impacting quality of life. Recognition of a bleeding disorder as the cause is often delayed. Management of bleeding complications is heterogeneous due to lack of treatment guidelines. Harmonizing severity classification of FVII deficiency may help standardize treatment strategies and development of specific guidelines for these women.

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blood coagulation disorders, gynecology, heavy menstrual bleeding, menorrhagia, obstetrics, postpartum hemorrhage

1 | INTRODUCTION

Factor VII (FVII) is a vitamin K-dependent procoagulant factor that when active (FVIIa) initiates blood coagulation through an interaction with tissue factor in the vessel wall during injury, activating factor X, resulting in formation of a cross-linked fibrin clot.[1] Congenital FVII deficiency is more common than previously thought; the UK National Haemophilia Database indicates an incidence of 1 in 50000.[2] The clinical phenotype of FVII deficiency is heterogeneous, ranging from asymptomatic; through minor bleeding symptoms including bruising, gum bleeding, and epistaxis; to major bleeding involving the central nervous system and gastrointestinal tract. Symptom range and severity varies even between individuals with a similar FVII activity (FVII:C) level.[3,4]

For women ("women" refers to women and girls in this article) with FVII deficiency, additional challenges include menstruation, ovulation, and parturition.[4] Other gynecological conditions like uterine fibroids are more likely to be symptomatic because of the increased bleeding tendency.[4] There is also some evidence that FVII levels may vary throughout the menstrual cycle, being lower during the luteal phase.[5]

For women without FVII deficiency, FVII levels normally rise during pregnancy, particularly during the third trimester. Women heterozygous for variants causing FVII deficiency show a more modest increase, while women homozygous for these variants generally do not show this increase.[4,6] Thrombosis has also been reported in patients with FVII deficiency, associated with treatment (e.g., factor replacement therapy or hormonal treatment).[7]

Due to the rarity of FVII deficiency, no large-scale studies of gynecological and obstetric problems in women with FVII deficiency exist. In this systematic review, we gathered data from case reports and studies of women with FVII deficiency to address the following points: the prevalence and management of bleeding symptoms, particularly heavy menstrual bleeding (HMB); the impact of HMB on quality of life (QoL); the effect of FVII deficiency on pregnancy outcomes; prevalence and management of postpartum hemorrhage (PPH); and the frequency of thrombotic complications in women with FVII deficiency. We also discuss treatment guidelines available in the literature.

Essentials

- Women with factor VII (FVII) deficiency are at risk of gynecological bleeding and postpartum hemorrhage.
- Thrombosis has been reported in women with FVII deficiency who have additional risk factors.
- This systematic review evaluated bleeding symptom prevalence and management in these women.
- Specific management guidance and clarity regarding severity of FVII deficiency are lacking.

2 | METHODS

This article was developed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA guidelines for systematic reviews. Databases (BIOSIS Previews, Current Contents Search, Embase, and MEDLINE) were searched for studies reporting FVII deficiency and gynecological or obstetric issues in women on March 8, 2021. As FVII deficiency is rare, no publication date limits were applied to ensure all relevant studies were captured. Conference proceedings, articles not written in English, and animal studies were excluded as part of the automated search.

The resulting abstracts were screened manually by two reviewers. Articles reporting genetic mapping only and articles that do not report bleeding symptoms in women with FVII deficiency were also excluded. Quality assessment was carried out by two independent reviewers using the Joanna Briggs Institute Critical Appraisal Tools.[8] The full text of the articles was reviewed, and if 50% of relevant criteria were met the publication was included. The authors had final approval of the selected articles and resolved any conflicts between the judgment of the reviewers. Data on bleeding symptoms and reported pregnancies were extracted from the selected articles. Full data extraction terms are included in Supporting Information. Terms previously used to describe HMB (e.g., metrorrhagia and menorrhagia) were included in our search and referred to in this article as "heavy menstrual bleeding/HMB." Treatment guidelines were also gathered from articles tagged as "reviews" retrieved by the search.

In line with a recent analysis including data from 728 patients that showed 92% of 154 patients with severe bleeding tendency had FVII:C levels below 5%, severity of FVII deficiency was classified as follows:[9] severe: <5% or <5 IU/dl; non-severe: ≥5% or ≥5 IU/dl and <65% or <65 IU/dl. The normal range varies depending on the reagents and methods used but is approximately 50–150 IU/dl. Although the range in % is often similar, these units are not interchangeable as the standard is different.

3 | RESULTS

The search recovered 765 abstracts. Excluding congress proceedings and animal studies left 414 abstracts. Following abstract review, full text review and quality assessment, 62 relevant studies were identified. Details of the review and exclusion process are shown in Figure S1 in supporting information.

3.1 | Baseline characteristics

From the 62 publications, 57 were research articles, including case reports (n = 31), case series (n = 12), prevalence studies (n = 5), quasi-experimental studies (n = 4), cross-sectional studies (n = 2), case–control studies (n = 2), and one cohort study. Data were available for 114 women. Severe FVII deficiency was observed in 45 women. The remaining articles were tagged as reviews and included relevant management guidelines (n = 5).

Table 1 shows baseline characteristics. Median age at diagnosis was 16.5 years (n = 22). Only seven women were assessed for consanguinity and, among these, consanguinity was recorded in three cases, two of whom had parents that were first cousins.[10–14] One woman assessed for consanguinity had non-severe FVII deficiency;[13] the other six had severe deficiency, including all three women for whom consanguinity was recorded.[10–12,14]

Bleeding symptoms were noted in family members of 12 women.[10,13,15–20] Five of these women were classified as having severe FVII deficiency[10,18] and five non-severe deficiency,[13,15–17] while FVII:C was not stated for the remaining two women.[19,20] Two women were reported as double heterozygous for Thr384Met and Arg413Gln variants of FVII, with 20% FVII activity.[13]

3.2 | Bleeding symptoms in women with FVII deficiency

Bleeding symptoms reported in women with FVII deficiency are shown in Figure 1. HMB was reported in 94 women (82%);[10,11,13,15–18,20–45] of these women, 37 had severe FVII deficiency,[7,10,11,16,18,25,26,28,30,34–36,41,42,44] 19 had non-severe def iciency,[7,13,15–17,24,27–29,32–34,41,42] and severity was not reported

TABLE 1 Demographic characteristics of women with congenital FVII deficiency

Demographic characteristic	Patients (n = 114)	References
Age at diagnosis, median (range), years (n = 22 patients)	16.5 (birth–47)	[10,11,13,17,19,20,36,40,41,44–46,55,59]
Consanguinity, n/7 patients[a]	3	[11,12,14]
Number of patients with bleeding symptoms in family members	12	[10,13,15–20]
Classification of FVII deficiency (n = 69 patients)		
Severe (<5% activity), n (%)	46 (67)	[7,10–12,14,16,18,25,26,28,30,34–36,41,42,44,46,47,51,55]
Non-severe (≥5% activity), n (%)	23 (33)	[7,13,15–17,24,27–29,32–34,41,42,56,59]
Country of origin (n = 92)		
Argentina	2	[13]
Bulgaria	1	[35]
Chile	1	[17]
China	1	[40]
Egypt	1	[12]
Germany	1	[36]
India	34	[28,38,39,41–43]
Iran	3	[31]
Ireland	1	[44]
Israel	1	[26]
Italy	5	[27,30,56]
Korea	1	[55]
Netherlands	1	[32]
Oman	1	[14]
Pakistan	2	[20,59]
Poland	1	[25]
Spain	1	[51]
Switzerland	3	[10]
Turkey	11	[19,22,24,29,37,45,47]
UK	7	[33,46]
USA	14	[11,15,16,18,21]

Note: Characteristics were not reported for every patient or were reported incompletely in some cases.

[a]A total of seven patients were assessed for consanguinity.Abbreviation: FVII, factor VII.

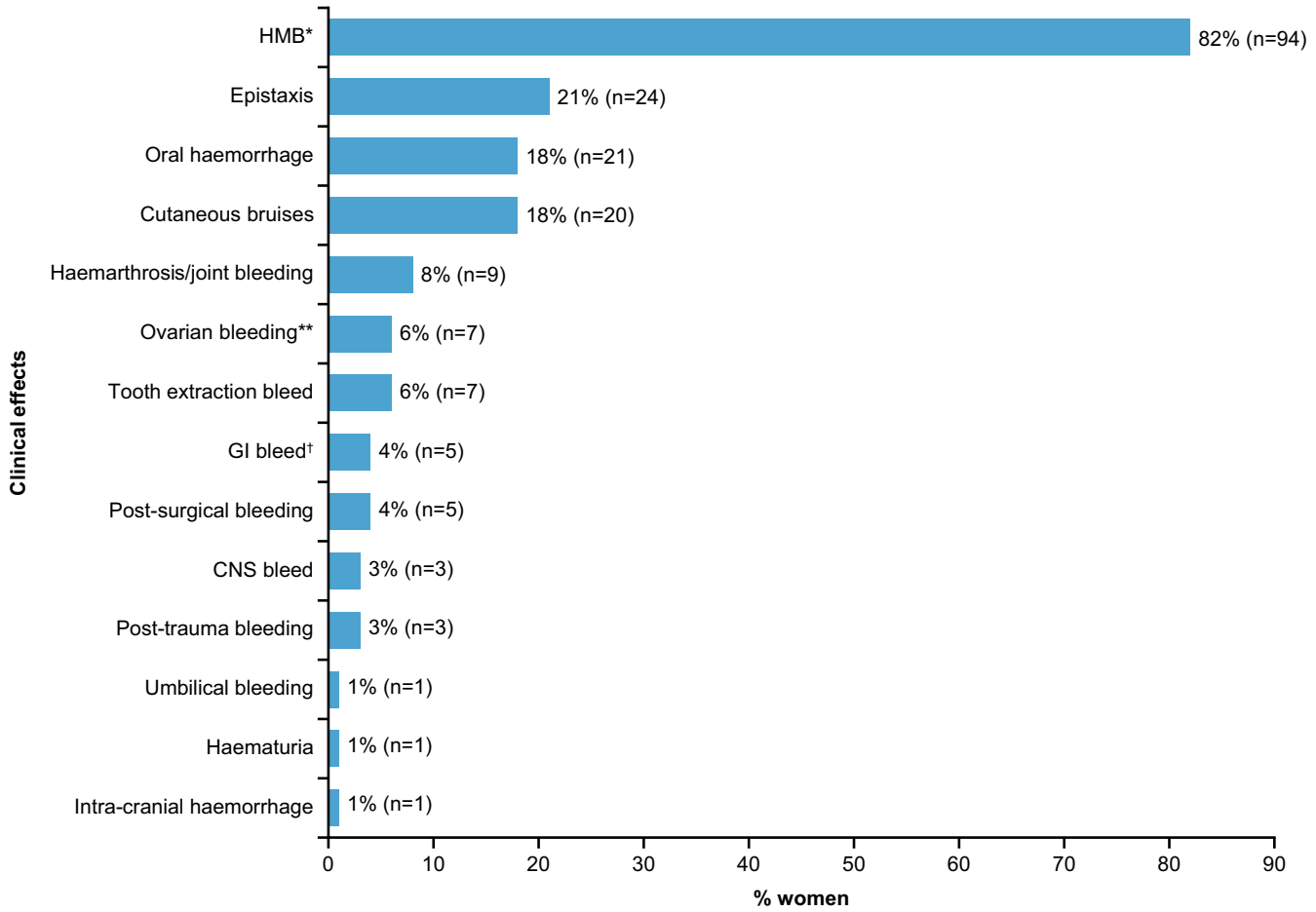

FIGURE 1 Clinical effects observed in women with congenital FVII deficiency. *Of 11 women assessed by PBAC, all 11 were confirmed as having HMB (score >100).[24,29,31,33] **Includes ovarian hemorrhage, peritoneal bleeding/hemorrhage, ovulation bleeding, hemorrhagic ovarian cyst, intraperitoneal bleeding/hemorrhage/hematoma, corpus luteum cyst/bleeding. †Includes melena and hematemesis. The percentages will not add up to 100% as women may experience multiple bleeding symptoms. CNS, central nervous system; FVII, factor VII; GI, gastrointestinal; HMB, heavy menstrual bleeding; NA, not applicable; PBAC, pictorial blood assessment chart

for the remaining 38.[19–23,31,33,37–40,43,45] HMB was confirmed by pictorial blood assessment chart (PBAC; score >100) in 11 cases.[24,29,31,33] Acute episodes in which HMB was a presenting symptom that required hospitalization were reported in 16 (14%) women, detailed in Table 2.[10,15,20,22,23,25,26,30,33,35,36,44]

Ovarian bleeding was reported in seven women (6%) (Table 3); six had severe FVII deficiency and one non-severe deficiency.[15,25,34,41,46] Hospitalization and blood transfusion was reported for one case.[15] Although detailed information was presented for only three women who experienced ovarian bleeding, all three had a history of other bleeding episodes; acute HMB requiring blood transfusions in two cases and hemarthrosis managed with recombinant FVIIa (rFVIIa) in one case.[15,25,46]

After HMB, the most frequently observed symptoms were epistaxis (21%), oral hemorrhage (18%), and bruising (18%; Table 1).

Iron-deficiency anemia was observed in 17 women (15%), associated with Plummer–Vinson syndrome in one case;[10,15,16,20,25,26,33,35,44] 15 of these women had HMB. Only two women with anemia did not report HMB, including one who only exhibited anemia during pregnancy.[12,16]

3.3 | Treatment of HMB

HMB treatments were described for 41 women ,[10,11,13,15,20–25,27,30,33–36,41,44] 21 of whom were severely FVII deficient.[10,11,16,25,26,30,34–36,41] All 16 patients with acute HMB (i.e., requiring hospitalization, surgery, or blood transfusion) are included in Table 2; this describes all treatments used to manage each patient as the case studies did not necessarily order the treatments chronologically. Of the 16 women admitted acutely with HMB, 10 (9%) received blood transfusions[10,15,20,22,25,26,33,35,44] and 6 (5%) required surgical intervention (curettage alone [$n = 2$], curettage followed by hysterectomy [$n = 1$], endometrial ablation [$n = 2$], and curettage followed by unspecified uterine surgery [$n = 1$]).[10,20,25,26,30,44] In four cases, a combination of multiple blood transfusions and surgical interventions was required.[20,25,26,44] One publication reported the use of methylergobrevin as treatment for HMB in one woman more than 20 years ago.[36]

Factor replacement was used in 19 (46%) cases (included use of intravenous rFVIIa in 14 cases), with variable duration and dose

TABLE 2 Acute HMB in 16 women with congenital FVII deficiency requiring hospital admission

	FVII:C level	Clinical history	Patient management	Reference
1	<1%	History of easy bruising and HMB	Curettage	[10]
2	<1%	History of epistaxis and HMB	Blood transfusion	[10]
3	Not reported	HMB	Blood transfusion, combined oral contraceptive	[22]
4	Not reported	HMB	Blood transfusion, combined oral contraceptive	[22]
5	Not reported	HMB	Combined oral contraceptive (unclear whether initial blood transfusion was required)	[22]
6	Not reported	HMB	rFVIIa (IV)	[23]
7	Not reported	HMB	rFVIIa (IV)	[23]
8	<1%	HMB and severe anemia, curettage led to diagnosis of simple endometrial hyperplasia, intraperitoneal bleeding identified during hysterectomy and recurred after hysterectomy	rFVIIa (IV); TXA; combined oral contraceptive; oral progesterone-only treatment; multiple blood, plasma, and platelet transfusions; curettage; hysterectomy (followed by rFVIIa [IV] and oral iron supplementation for intraperitoneal bleeding)	[25]
9	2%	HMB and anemia	Regular blood transfusions, curettage, combined oral contraceptive, oral TXA, and oral gonadotropin-releasing hormone analogue (all ineffective), followed by thermal balloon endometrial ablation	[26]
10	3%	HMB associated with multiple fibromas of the uterus	Curettage, gonadotropin-releasing hormone analogue (implant), oral iron supplementation, uterine surgery	[30]
11	36%	History of HMB and anemia (later also diagnosed with Plummer-Vinson syndrome)	Blood transfusions, iron supplementation (oral/IV), combined oral contraceptive, hormonal intrauterine device	[15]
12	42 IU/dl	HMB	Blood transfusions	[33]
13	2%	HMB and anemia	Iron supplementation, blood transfusions	[35]
14	1%	HMB (admitted twice)	Prothrombin complex concentrate (IV), methylergobrevin, combined oral contraceptive, then rFVIIa (IV) (when it became available)	[36]
15	<0.01 IU/dl	HMB and anemia	TXA, continuous iron supplementation, intermittent red cell transfusion, rollerball endometrial ablation (with rFVIIa [IV] for surgery/recovery)	[44]
15	2.4%	HMB and anemia	Blood and platelet transfusions, fresh frozen plasma (IV), progesterone-only treatment, TXA, oral NSAIDs, iron supplementation, curettage	[20]

Note: All treatments listed for each patient, as division between treatments received at acute admission and during ongoing treatment were not always separated. Routes of administration were not always specified.

Abbreviations: a, active; C, control plasma; FVII, factor VII; HMB, heavy menstrual bleeding; IV, intravenous; NSAID, non-steroidal anti-inflammatory drugs; TXA, tranexamic acid.

of treatment.[23,25,34,36,44] Intravenous plasma-derived FVII concentrate was used in four cases[10,11,13,34] and fresh frozen plasma (FFP) in two cases.[20,25] Other hemostatic treatments included antifibrinolytics such as oral tranexamic acid (TXA; five cases, 12%)[20,24–27] and intravenous prothrombin complex concentrate (one case, 2%).[36]

Hormonal treatments included combined oral contraceptives (n = 10),[13,15,16,22,25–27,36] progestogen-only treatment (n = 3),[10,20,25] and hormonal intrauterine devices (n = 3).[15,21] Two women were treated with a gonadotropin-releasing hormone analogue.[26,30] In six of these cases, hemostatic and hormonal treatments were used; in four women this continued long term and in two cases hormonal treatment was used long term.[10,13,20,25,26,36]

3.4 | Effect of HMB on QoL

Only one study explicitly addressed the effect of HMB on QoL, comparing QoL outcomes between 14 women with FVII deficiency and 23 controls.[33] General health scores, health and daily activity scores, dysmenorrhea, and median QoL score were significantly worse in women with FVII deficiency versus controls.

TABLE 3 Ovarian bleeding in 7 women with congenital FVII deficiency

	FVII:C level	Clinical history	Management of ovarian bleeding	References
1	<1%	Frequently admitted to hospital due to HMB and severe anemia, curettage led to diagnosis of simple endometrial hyperplasia, intraperitoneal bleeding identified during hysterectomy and recurred after hysterectomy	rFVIIa (IV), iron supplementation	[25]
2	36%	History of HMB, anemia, and dysphagia, admitted to hospital due to anemia and blood in stools, hemorrhagic cyst in ovary and esophageal webs identified leading to diagnosis of Plummer–Vinson syndrome and FVII deficiency	Red cell transfusion, iron supplementation	[15]
3	<1%	Bruising, hemarthrosis, hemoperitoneum, and HMB reported	Not reported	[34]
4	<1%	Bruising, epistaxis, gum bleeding, hemoperitoneum, hemorrhoidal bleeding, and HMB reported	Not reported	[34]
5	4%	Hemoperitoneum reported	Not reported	[34]
6	2 IU/dl	History of hemarthrosis, presented with corpus luteum bleeding	rFVIIa (IV), combined oral contraceptive	[46]
7	4%	History of spontaneous bruising and hemoperitoneum	Fresh frozen plasma (IV)	[41]

Abbreviations: a, active; FVII, factor VII; HMB, heavy menstrual bleeding; IV, intravenous; r, recombinant.

3.5 | Pregnancy and FVII:C levels

A total of 58 pregnancies in 41 women were reported in the retrieved literature.[10–12,14,16–20,23,35,36,40–42,47–58] FVII:C levels were reported before or during early pregnancy in 18 women; seven had severe FVII deficiency.[11,14,16,17,19,36,47–52,55,56] Three studies measured changes in FVII:C levels in 11 pregnancies.[16,17,53] Increased FVII activity was observed in the third trimester compared to baseline level in 10 pregnancies, all in women with non-severe deficiency;[16,17,53] no rise was observed in one woman with severe deficiency.[16]

3.6 | Bleeding symptoms and treatment during pregnancy

Eleven women reported bleeding symptoms during pregnancy[11,16,19,20,36,48–50,52] (Table 4); four had severe FVII deficiency,[16,20,36,49] six had non-severe FVII deficiency,[11,16,19,48,50,52] and severity was not reported for one woman.[52]

Vaginal bleeding was reported in four women (two with severe FVII deficiency and two with non-severe FVII deficiency)[19,36,49,50] including one case of retroplacental hematoma in a woman with vaginal bleeding from 5 weeks.[36] One woman had bleeding episodes at 22 weeks and 39 weeks, the second episode was prior to delivery;[49] one woman experienced a bleeding episode at 26 weeks following an automobile accident;[50] and another had a bleeding episode associated with pain prior to a pre-term delivery at 29 weeks.[19]

Treatments to manage bleeding symptoms during pregnancy were reported for four pregnancies.[16,20,36,52] One woman received continuous prophylaxis with daily off-label intravenous rFVIIa throughout pregnancy (30 μg/kg every 8 hours).[36] Despite this, recurrent hematomas and vaginal bleeding occurred. These episodes were managed by increasing the rFVIIa dose, the highest exposure being a 30 μg/kg dose every 6 h for 2 days to treat a specific retroplacental hematoma during week 6 of pregnancy; this was subsequently reduced.[36] One woman experienced gastrointestinal bleeding at 10 weeks, caused by esophageal and fundal varices, and was treated with band ligation and platelet and red cell transfusions.[52] Intravenous FFP was used to treat two episodes of hematuria in one woman at 27 weeks.[20] Finally, one woman developed anemia and was treated with intravenous iron.[16]

TABLE 4 Bleeding symptoms during pregnancy in women with congenital FVII deficiency

	Pregnancies ($n = 58$)	
Bleeding symptom	Patients, *n* (%)	References
Epistaxis	4 (7)	[11,16,52]
Oral hemorrhage	1 (2)	[11]
Cutaneous bruises	1 (2)	[52]
GI bleed[a]	1 (2)	[52]
Post-trauma bleeding	2 (3)[b]	[16,50]
Hematuria	2 (3)	[20,48]
Vaginal bleeding[b]	4 (7)	[19,36,49]
Retroplacental hematoma	1 (2)	[36]

Abbrveiations: FVII, factor VII; GI, gastrointestinal.

[a]Includes melena and hematemesis.

[b]Includes one instance of vaginal bleeding following an automobile accident.

3.7 | Pregnancy outcomes

Outcomes were reported for 53 pregnancies (Table 5). There was one elective abortion.[53] Six miscarriages were reported from two studies.[19,53] One study reported five miscarriages from seven pregnancies in the same woman (all associated with excessive vaginal bleeding); one occurred at 16 weeks and the other four at

TABLE 5 Pregnancy outcomes in women with congenital FVII deficiency

	Pregnancies ($n = 58$)	References
Pregnancy outcome, *n* (%)		
Miscarriage (2 women)[a]	6 (10)	[19,53]
Surgical termination (1 woman)	1 (2)	[53]
Delivery of live infant (38 women)	46 (79)	[10–12,14,16–20,35,36,40,48–58]
Outcome not reported (5 women)	5 (9)	[7,23,41,42]
Prematurity, *n* (%)[b]	3 (5)	[14,16,19]
Birth weight, median (range), g[c]	3215 (1020–3800)	[14,17–20,35,47–50,54–58]

[a]Includes one surgical evacuation.

[b]Gestational age reported for 26 pregnancies; prematurity defined as birth before 37 weeks gestational age.

[c]Birth weight reported for 19 births.

10 weeks.[19] The sixth miscarriage in a different patient required surgical evacuation associated with excessive blood loss, although blood transfusion was not required.[53]

A total of 46 pregnancies reached viability, including one delivery of twins.[11,12,14,16–20,35,36,40,48–58] Outcomes and delivery methods were unreported for the remaining five pregnancies,[7,23,41,42] thus 45 deliveries were reported in total. Mode of delivery was recorded for 44 deliveries. There were 22 vaginal[11,14,16,18,35,36,40,49,50,53,56–58] and 22 caesarean deliveries.[12,16,17,19,20,23,47,48,51–55] Ten emergency caesarean deliveries were performed for reasons including failure to progress or failed induction of labor (six cases),[16,47,48,53,54] fetal distress (three cases),[17,19,20] and breech presentation (one case).[55] Three caesarean deliveries were planned; one to reduce risk of human immunodeficiency virus transmission to the fetus,[51] one due to prior maternal intracranial hemorrhage,[53] and one at maternal request.[53] The rationale for the remaining eight caesarean deliveries was not reported.[12,16,19,52,53]

3.8 | Prophylaxis prior to delivery

Prophylactic treatment was administered prior to delivery in 33 deliveries in 31 women (14 vaginal deliveries, 15 caesarean deliveries, and 2 cases with mode of delivery not reported); in 16 cases, the women had severe FVII deficiency. Treatments used included intravenous rFVIIa in 16 cases,[16,23,35,36,47,49,51,53,56,57] plasma-derived FVII in five cases,[11,18,20,58] and FFP in seven cases.[12,14,17,19,20,50,55] Other prophylactic treatments included oral TXA (four cases)[16,17,57] and platelet transfusion (three cases).[17,48,52]

3.9 | Anesthesia and analgesia

Anesthesia and analgesia use was reported in 19 deliveries from 17 women; three mothers had severe FVII deficiency. Neuraxial block was used before caesarean delivery in eight cases (one woman with severe FVII deficiency, six with non-severe deficiency, and one with unreported severity)[12,53,54] and prior to vaginal delivery in one case (non-severe FVII deficiency).[16] Neuraxial block was preceded by hemostatic treatment in four cases; rFVIIa in three cases[53] and FFP in one case[12] with no TXA used. There were six uses of general anesthesia for caesarean delivery (one woman with severe FVII deficiency and five with non-severe deficiency);[16,17,48,55] in four cases, FVII deficiency was a deciding factor in the choice to use general anesthesia.[16,17,48] Hemostatic treatments used before general anesthesia comprised TXA (three cases),[16,17] FFP (two cases),[17,55] platelet infusion (two cases),[17,48] and rFVIIa (one case),[16] including combinations of these treatments.[16,17] Remifentanil, a short-acting synthetic opioid analgesic, was used intravenously for patient-controlled analgesia for two vaginal deliveries (one woman with severe FVII deficiency and one with non-severe deficiency); FVII deficiency was a deciding factor in one case.[55]

3.10 | Bleeding during delivery

Estimated blood loss during delivery was reported for ten deliveries from eight women, with a mean of 900 ml (range 400–1800 ml).[16,18,20,53] As shown in Table 6, primary PPH was reported for 12 deliveries in 11 women (27%; four women with severe FVII deficiency and seven women with non-severe deficiency);[16–19,40,53,57] reported causes included uterine atony (four cases),[16,17,57] first- and second-degree lacerations (four cases),[16,18] placental abruption (one case),[19] and intraoperative bleeding associated with caesarean delivery (three cases).[16,19,53]

Of the women who experienced PPH, eight (62%) received prophylaxis prior to delivery. Prophylactic treatment included rFVIIa (four cases),[16,53,57] TXA (three cases),[16,17] plasma-derived FVII concentrate (one case),[18] FFP (one case),[17] and platelet transfusion (one case).[17]

Treatment for PPH was reported in eight cases (67%) and included hemostatic treatments: intravenous FFP (two cases),[16,17] oral TXA (two cases),[16] intravenous rFVIIa (one case),[16] and intravenous

TABLE 6 Postpartum hemorrhage in women with congenital FVII deficiency

	FVII:C level	Prophylaxis prior to delivery	Delivery	Postpartum hemorrhage	Management of postpartum hemorrhage	Reference
1	30 IU/dl baseline/60 IU/dl at term	rFVIIa (IV)	Caesarean delivery under epidural	1400 ml blood loss	Not stated	[53]
2	1% baseline/<1% third trimester	rFVIIa (IV)	Vaginal delivery at 38 weeks with remifentanil patient-controlled analgesia (induced due to pre-eclampsia)	Second-degree laceration, 800 mL blood loss	Not stated	[16]
3	10% baseline/16% third trimester	None	Caesarean delivery at 38 weeks under general anesthesia (induced due to oligohydramnios, induction failed)	Uterine atony, 1000 ml blood loss	Misoprostol (oral), hemabate (IM), TXA	[16]
4	7% baseline/16% third trimester	TXA, rFVIIa (IV)	Caesarean delivery at 38 weeks under general anesthesia (induced due to gestational hypertension, induction failed)	Uterine atony, 800 ml blood loss	Misoprostol (oral), hemabate (IM)	[16]
5	28% baseline/68% third trimester	None	Vaginal delivery at 38 weeks under epidural	Second-degree laceration, 500 ml blood loss	Not stated	[16][a]
5	28% baseline/64% third trimester	None	Vaginal delivery at 39 weeks with remifentanil patient-controlled analgesia	First-degree laceration, 600 ml blood loss	Not stated	[16][a]
6	29% baseline/38% third trimester	TXA	Caesarean delivery at 36 weeks under general anesthesia (hospitalized due to cholestasis)	1800 ml blood loss	Packed red blood cells, FFP (IV)	[16]
7	3 IU/dl third trimester	rFVIIa (IV)	Delivery at 38 weeks (mode of delivery not specified)	Uterine atony	Oxytocin infusion, misoprostol (oral), ergotamine, carboprost (IM), packed red blood cells; then oral TXA for 10 days	[57]
8	5% first trimester/9% third trimester	Platelets, FFP (IV), TXA, uterotonics	Caesarean delivery at 39 weeks under general anesthesia (due to suspected foetal distress)	Uterine atony	Red cells, FFP (IV), platelets, oxytocin (IV), ergomovine, misoprostol, carbetocin (IV), transmural uterine compression sutures; FFP and platelets were continued for 5 days	[17]
9	1.7% third trimester	Plasma-derived FVII concentrate (IV)	Vaginal delivery at 39 weeks	400 ml blood loss	Plasma-derived FVII concentrate (IV) continued for 3 days	[18]
10	3.6% baseline	None	Vaginal delivery	Massive vaginal bleeding	Blood transfusion	[40]
11	46% second trimester	None	Caesarean delivery at 29 weeks (due to vaginal bleeding and foetal bradycardia)	Placental abruption 900 ml blood loss	Crystalloid/colloid solutions (IV); FFP and red blood cells for post-operative anemia	[19]

Note: Route of administration was not specified in every case.

Abbreviations: a, active; FFP, fresh frozen plasma; FVII, factor VII; IM, intramuscular; IV, intravenous; r, recombinant; TXA, tranexamic acid.

[a]Postpartum hemorrhage was reported for two pregnancies in the same woman.

plasma-derived FVII concentrate (one case),[18] or inducing uterine contraction (four cases),[16,17,57] with uterotonic agents including oxytocin infusion, and intramuscular ergotamine and prostaglandins. Blood transfusion was required in five (42%) PPH cases.[16,17,19,40,57]

Secondary PPH was reported in one woman (2%) with severe FVII deficiency;[35] hemorrhage occurred when sutures were removed from the infected episiotomy site. This was treated with intravenous rFVIIa and local and systemic antibiotics.

3.11 | Neonatal outcomes

There were 46 live newborns including one set of twins, and no neonatal death. Neonatal birth weight was reported in 18 cases.[14,17–20,35,47–50,54–58] Median birth weight was 3215 g.

There were three pre-term deliveries (prior to 37 weeks of gestational age).[14,16,19] One was at 29 weeks following hospital admission for sudden pelvic pain and vaginal bleeding;[19] this infant was hospitalized due to prematurity, with no reported neonatal bleeding complications. The other two pre-term deliveries were both at 36 weeks.[14,16] No additional neonatal complications were reported in the retrieved literature. Of 46 live neonates, 2 had their FVII level measured. One had FVII:C 14% at 2 weeks of age, but it is unclear if this persisted into infancy. The other had a normal level.[49,50]

3.12 | Incidence of thrombosis in women with FVII deficiency

Seven thrombotic events were reported in six women (5%; one with severe FVII deficiency and five with non-severe FVII deficiency).[7,52,59] Two incidences occurred following hysterectomy, including one incidence of disseminated intravascular coagulation in a woman who had received prothrombin complex concentrate and plasma-derived FVII, and one incidence of deep vein thrombosis in a woman who had received plasma-derived FVII concentrate and prothrombin complex concentrate.[7] Thrombosis was reported in one individual during two separate pregnancies.[52] The first was a portal vein thrombosis that was an incidental finding during a computed tomography scan to investigate thrombocytopenia. The woman was treated with low molecular weight heparin for 5 months; this was discontinued due to increased bleeding episodes (epistaxis, rectal bleeding, HMB, and ecchymoses). During the second pregnancy, esophageal and fundal varices developed due to cavernous transformation of the portal vein; as detailed above, this was treated by band ligation, platelet transfusion, and red cell infusion. One woman developed superficial venous thrombosis postpartum; this woman had asymptomatic non-severe FVII deficiency and had not received FVII replacement therapy.[7] There was one incidence of cerebral venous sinus thrombosis in a 40-year-old woman who had been receiving norethisterone 5 mg three times per day; she was also assessed for thrombophilia markers but all were within normal ranges.[59] The final reported incidence was an apparently spontaneous cerebral infarction, which had no association with surgery, pregnancy, or replacement therapy.[7]

3.13 | Guidelines for the diagnosis and management of FVII deficiency gathered from the literature

FVII deficiency is indicated by prolongation of the prothrombin time, a normal activated partial thromboplastin time, and confirmed by specific assays for FVII clotting activity and antigen.[60] Guidelines for management of FVII deficiency were retrieved from five articles; however, three focused on women with rare bleeding disorders generally and one on FVII deficiency in men and women, highlighting the lack of detailed consensus guidance for management of women with FVII deficiency. Additionally, none of the five articles contained guidance regarding identification of women at most risk of gynecological and obstetric bleeding symptoms.

In terms of gynecological bleeding, hormonal or antifibrinolytic treatments were considered sufficient to manage HMB.[61] Management of HMB-associated anemia was also considered important.

In terms of pregnancy in women with FVII deficiency, recommendations regarding prophylaxis use varied, and its use should be decided based on factor levels, bleeding history (as factor levels do not correlate with symptom severity), and mode of delivery, as surgical delivery methods such as caesarean section may require prophylaxis.[6,62,63] Additionally, increases in FVII levels are often observed in women with mild deficiency, so measurement of FVII activity in the third trimester is particularly important in defining the need for prophylaxis in these patients.[6] Prophylactic options recommended in the publications are plasma-derived intravenous FVII and off-label rFVIIa, with a dose of 15–30 μg/kg recommended to cover delivery, although it has been successfully used with various regimens in specific cases.[35,49,51,63] Only one article recommended TXA to control PPH[6] and only one recommended delivery in a specialist center.

4 | DISCUSSION

This systematic review demonstrates that women with FVII deficiency are at risk of gynecological and obstetric bleeding complications, and that these are not always effectively managed. This is partly because no specific treatment guidelines exist for women with FVII deficiency; treatment recommendations were derived from general bleeding disorder guidance briefly covering FVII deficiency, and expert opinions/review articles. An important factor impacting treatment variability between cases is a lack of consensus on what FVII:C level constitutes severe deficiency. In this analysis, we used a cut-off of <5% (approximately equivalent to 5 IU/dl) based on a recent publication demonstrating that severe bleeding symptoms were mostly observed in patients with <5%;[9] however, other

articles suggest other cut-offs, often based on the factor levels used in hemophilia.

Other measures for severity have been suggested, incorporating clinical symptoms and *F7* variant zygosity. Mariani and colleagues proposed an empirical classification system based on presentation of bleeding symptoms; patient genotypes did not correlate with particular bleeding phenotypes, even in different patients homozygous for identical *F7* variants.[3] Additionally, patients with low FVII:C did not necessarily suffer from the most severe bleeding symptoms.[6] Finding a universally acceptable definition of severity is difficult in the absence of measurements that correlate with clinical phenotype.

HMB was the most common bleeding symptom identified in the review, reported in 82% of women; 14% had an acute HMB episode requiring hospitalization and urgent medical/surgical interventions, with 9% requiring a blood transfusion. Although some serious non-gynecological bleeding events occurred (e.g., intracranial hemorrhage and gastrointestinal bleeding), other bleeding events were relatively minor, with epistaxis being the most common. This aligns with a previous analysis of men and women with FVII deficiency.[3] The identified HMB rate is much higher than in the general population (10–35%), and aligned with the high frequency observed in women with other inherited bleeding disorders including von Willebrand disease (74%), hemophilia carriers (57%), and factor XI deficiency (59%).[64] HMB was the primary cause of anemia in these women and reported in 37% of those with HMB. This significantly affects work, education, and social activities, and if untreated may have a detrimental effect on mental well-being.[33] The paucity of QoL data for women with FVII deficiency suggests that more analysis of this population is needed to better understand their needs.

Our finding regarding median age at diagnosis (16.5 years) indicates that women experience significantly delayed diagnosis, which is unfortunately an issue for women with mild bleeding disorders generally. Considering the average age of menarche is 12 years, and that HMB occurs in more than 80% of women with FVII deficiency, this indicates that affected women on average remain undiagnosed and untreated for 4 years after menarche. Greater awareness of HMB and early consideration of the possibility of an underlying bleeding disorder is required among patients and health-care professionals.

Ovarian bleeding arising from ovulation was reported in seven (6%) women in this review;[15,25,34,41,46] similar rates were observed in women with other rare bleeding disorders.[65] Ovarian bleeding can be serious, internal bleeding that is not readily visible and challenging to manage. Surgery, potentially including oophorectomy, may be required to control the bleeding, compromising the woman's future fertility. Increased awareness and identification of at-risk women may prevent future episodes. Prevention of bleeding due to ovulation is by suppression of ovulation with combined hormonal contraceptives, or prophylactic hemostatic treatment for those who wish to become pregnant. When bleeding does occur, close collaboration between hematology and gynecology teams is required for optimal management.

Based on our results, FVII deficiency apparently does not increase the risk of vaginal bleeding, miscarriage, or antepartum hemorrhage during pregnancy. However, conclusions are limited due to lack of adequately powered studies. Of the 53 pregnancies with reported outcomes, there were only six miscarriages (four during the first trimester),[19,53] in line with established miscarriage rates of approximately 20% in the overall population.[66] Therefore, there is no apparent need for prophylactic treatment during pregnancy. The Royal College of Obstetricians and Gynaecologists (RCOG) guideline for management of women with inherited bleeding disorders contains some recommendations specific to severe FVII deficiency. These suggest rFVIIa 15–30 μg/kg should be considered only in response to abnormal bleeding, with TXA for mild bleeding.[67] Interestingly, in one study a woman with severe FVII deficiency (<1%) received daily rFVIIa prophylaxis throughout pregnancy; however, vaginal bleeding and subchorionic hematomas occurred despite prophylaxis.[36]

No complications were identified among women who had undergone neuraxial block. However, general anesthesia was used for six caesarean deliveries (five with non-severe deficiency). This suggests that many women with FVII deficiency may be denied the option of neuraxial block based on their factor deficiency, despite its efficacy and safety and the fact that FVII deficiency can be corrected prior to delivery, particularly in the approximate one third of the overall patient population we identified with non-severe deficiency. Available guidelines recommend that use of neuraxial block should be decided on a case-by-case basis following discussion with a multidisciplinary team.[67–71]

Three publications highlighted the rise in FVII:C levels during pregnancy, in 10 pregnancies in women with non-severe FVII deficiency but not in the 1 woman who had severe deficiency.[16,17,53] According to available guidelines, it is important to assess bleeding risk during the third trimester to develop a multidisciplinary delivery plan.[71,72] Bleeding phenotype, FVII level, and obstetric issues should be assessed to manage delivery appropriately and minimize PPH risk.

Primary PPH occurred in more than 25% of the reported deliveries compared with lower rates in the general population (e.g., <10% in one UK study[73]). Additionally, blood transfusion was needed in 42% cases with PPH, suggesting that severe PPH is more likely in these women. Although some women with PPH had severe FVII deficiency, most reported non-severe deficiency. Interestingly, morethan half of the women with PPH had received prophylactic treatment prior to delivery. However, it is unclear whether these women received adequate risk assessment and prophylaxis. Consensus is lacking regarding the type of hemostatic agent, dose, and duration for prophylaxis during delivery in women with FVII deficiency. RCOG guidelines indicate that for women with FVII activity <0.2 IU/ml in the third trimester, who require caesarean delivery or who have a history of bleeding, off-label rFVIIa 15–30 μg/kg every 4–6 h for at least 3 days should be considered and for all other women with FVII deficiency, rFVIIa is only recommended in response to bleeding.[67] TXA is effective and commonly used for prevention and treatment of mild bleeding in rare bleeding disorders, including management of delivery. Its use is also recommended in combination with factor replacement for those at risk of severe bleeding.[67,71] Interestingly, there were only five reported uses of TXA for prevention or treatment of PPH in this review. Moreover, hemostatic prophylaxis alone does not necessarily prevent PPH, as PPH can be due to obstetric causes, most commonly uterine atony. A

TABLE 7 Recommendations from guidelines regarding management of rare bleeding disorders that include FVII deficiency in gynecological and obstetric settings

Country	Recommendations for gynecological treatment	Recommendations for pregnancy	Recommendations for labor and delivery
Australia	• Factor replacement and TXA may be indicated for invasive procedures such as oocyte retrieval, and these should be carried out in a multidisciplinary clinical setting with appropriate experience to manage complications	• Patients should have factor levels measured before planned conception • Specific antenatal therapy is not indicated	• Factor replacement should be organized before delivery if necessary and a multidisciplinary care plan developed • TXA should be used for surgical procedures and following miscarriage until bleeding settles • Delivery should be carried out in an obstetric unit with support from a specialist hemophilia center, with individualized care • Delivery method should be based on obstetric indications and not on presence of a rare bleeding disorder • Instrumental delivery should be avoided • TXA is indicated immediately before delivery, and 4 h post-delivery if there is PPH, and factor replacement if required • Regional anesthesia is contraindicated if factor levels cannot be normalized by treatment • To reduce PPH risk, factor levels should be maintained for ≥3 days following vaginal delivery and ≥5 days following caesarean delivery • If primary PPH occurs, factor replacement therapy may be appropriate. Secondary PPH should be managed acutely with TXA, and longer term with oral contraceptives or a levonorgestrel releasing IUD

USA[68,69]	• Women with inherited bleeding disorders should have access to specialist centers with multidisciplinary support as needed
	• Genetic counseling should be provided
	• HMB should be managed by multidisciplinary teams according to patient preference
	• Perioperative management should be developed for women undergoing invasive procedures
	• HMB should be managed by a multidisciplinary approach considering patient preferences
	  • Hormonal therapy (combined oral contraceptive or levonorgestrel-releasing IUD) or TXA is recommended
	  • Factor replacements should be available if needed
		• Pregnancy should be managed by a multidisciplinary team including coagulation specialists, obstetrician/gynecologist, and anesthesiologist
		• Early pregnancy procedures should be performed in settings where hemorrhage can be managed
			• Plan for management of childbirth should be in place before delivery
			• Delivery should take place in a center with consultation available from a coagulation disorder specialist, neonatologist, and full laboratory service support
			• Factor replacement products should be available for use at the clinic
			• Neuraxial anesthesia is to be used at the discretion of the treating physician following multidisciplinary discussion in advance of the patient's due date
			• Active management should be used during the third stage of labor to minimize blood loss. TXA can be used via the oral or IV routes

UK[67,70]	• Topical pro-hemostatic agents, endocrine therapy, and TXA can be used to manage HMB • For mild bleeding or minor surgery in higher bleeding risk cases, and for all bleeds and surgery in low bleeding risk cases, consider TXA 15–20 mg/kg or 1 g four times daily alone • For severe bleeding or major surgery in higher bleeding risk cases, consider rFVIIa 15–30 μg/kg repeated if required every 4–6 h, usually for a minimum of three doses (2B)		• Multidisciplinary management is required, with input from obstetricians and hematologists with expertise in the field, and considering maternal preferences • TXA should be administered at least 2 h before delivery to ensure peak plasma level at hemostatic challenge, and should be used in the case of miscarriage until bleeding settles • For delivery in women with FVII activity <0.2 IU/ml in the third trimester, who require caesarean delivery or who have a history of bleeding, consider off-label rFVIIa 15–30 μg/kg every 4–6 h for at least 3 d. For all other women with FVII deficiency, consider rFVIIa 15–30 μg/kg only in response to abnormal bleeding • Plasma derived FVII concentrate 10–40 IU/kg is an alternative if rFVIIa is not available • The choice of anesthesia used is at the discretion of the multidisciplinary team if factor levels can be normalized

TABLE 7 (Continued)

Country	Recommendations for gynecological treatment	Recommendations for pregnancy	Recommendations for labor and delivery
Canada	• Ideally, care for women with rare bleeding disorders is individualized and managed via multidisciplinary clinics • Hormonal treatments are recommended as first-line treatments (particularly in mild cases), including combined oral contraceptives, progesterone, and danazol. GnRHa not recommended due to side effects of bone loss and menopausal symptoms • Oral TXA can be used effectively during menstruation • For women who do not wish to conserve fertility, endometrial ablation is considered a conservative surgical option, with hysterectomy being considered definitive	• A multidisciplinary approach is required to manage pregnancy • Factor levels should be monitored prior to any diagnostic procedure, and measured during the third trimester (32–34 weeks) to develop an appropriate delivery plan	• Delivery should take place in a specialist center • Use of epidural and spinal anesthesia is contraindicated, due to risk of neuraxial hematoma • Use of regional anesthesia is not contraindicated and should be decided on a case-by-case basis • TXA and oral contraceptives recommended to treat secondary postpartum hemorrhage

Abbreviations: a, active; FVII, factor VII; GnRHa, gonadotrophin releasing hormone analogue; IUD, intrauterine device; IV, intravenous; PPH, postpartum hemorrhage; r, recombinant; TXA, tranexamic acid.

more comprehensive approach, focusing on adequate hemostasis and prevention of uterine atony through active management of placental delivery and use of appropriate uterotonics are crucial for prevention and management of PPH in these women.

Although thrombosis is described in patients with FVII deficiency, genome-wide association studies have not identified *F7* as a locus associated with thrombotic risk.[7,74] This would likely require an as yet undescribed gain of function variant. We identified seven cases of thrombosis in six women. Except for one spontaneous case, these occurred in a surgical context with replacement therapy, pregnancy, and hormonal contraception as potential risk factors.[7,52,59] The data indicate that FVII deficiency may not necessarily protect against thrombotic events.[7]

The observed treatment inconsistencies are likely due to factors including lack of standardized definitions and tests for severity of FVII deficiency, variability in bleeding symptoms even among patients with the same *F7* variants, and the relative rarity of FVII deficiency, resulting in few patients being part of prospective studies for new management protocols. Indeed, the findings of this review may be limited by these issues.

While our search revealed some guidelines for management of gynecological and obstetric symptoms in women with FVII deficiency, it is important to contrast these with established national-level guidelines, although in most cases these also refer to rare bleeding disorders generally without a focus on FVII deficiency (Table 7). The guidelines in the retrieved articles broadly align with those in national-level guidelines, with TXA being used for minor bleeding incidents[6] and factor replacement for specific bleeding incidents or when FVII activity is low during delivery.[61–63,75] There is an emphasis on individualized, multidisciplinary management of women with FVII deficiency, including obstetricians/gynecologists, hematologists, anesthesiologists, and laboratory teams, and access to care in expert centers, aligned with some of the retrieved guidance.[61] Setting up appropriate team structures and referral pathways is important to appropriately manage women with FVII deficiency and improve outcomes.

Our findings indicate that standardizing severity classification of FVII deficiency is a priority. This may require a combination of bleeding symptoms and plasma FVII:C levels. Additionally, appropriate assessment of the gynecological condition and obstetric risk factors in pregnancy may lead to better targeting of treatments for gynecological symptoms and proactive childbirth management. A multidisciplinary approach is required as women with more severe deficiency/symptoms could be directed to appropriate specialist centers more rapidly, with individualization of care based on overall patient status. This approach may also support targeted recruitment of patients into clinical trials.

5 | CONCLUSION

Women with FVII deficiency have a high risk of bleeding complications due to the hemostatic challenges posed by ovulation, menstruation, and childbirth. HMB is the most common bleeding symptom in women with FVII deficiency and impacts QoL, but few studies focus on this aspect and more information is needed. There is a wide range of management strategies that include hemostatic and hormonal treatments. PPH is a potential complication for pregnant women with FVII deficiency; joint obstetric and hematological care is needed to address the coagulation defect and manage potential obstetric causes of PPH. Standardizing definitions of severity of FVII deficiency may result in more uniform treatment strategies for these women; additionally, there may be further need to unify treatment guidelines once appropriate treatment strategies have been identified.

AUTHOR CONTRIBUTIONS

R. Abdul-Kadir and K. Gomez designed the search and data extraction strategy, reviewed the search results, analyzed the extracted data,

reviewed and wrote drafts of the paper, and approved the final version of the paper. The protocol for this review is registered at PROSPERO (https://www.crd.york.ac.uk/prospero/) with the registration CRD42021218888.

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CONFLICTS OF INTEREST

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Abbreviation: FVII, factor VII.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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