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Is prophylaxis required for delivery in women with factor VII deficiency?

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Abstract

Introduction—Factor VII (fVII) deficiency is a rare congenital bleeding disorder in which fVII activity level and bleeding tendency do not completely correlate. Pregnancy and delivery present a significant hemostatic challenge to women with fVII deficiency. Treatment with recombinant factor VIIa (rfVIIa) carries a thrombotic risk and the literature is unclear whether prophylaxis is necessary prior to delivery.

Aim—To define management, hemorrhagic and thrombotic complications of pregnant women with fVII deficiency through a systematic review.

Methods—Medical databases (PubMed, MEDLINE, CINAHL, Academic Search Premier, Cochrane Library, Web of Science and Scopus) were searched using “factor VII deficiency” and “pregnancy” or “surgery.” Overall 34 articles, 4 abstracts, and 3 institutional cases were reviewed.

Results—Literature from 1953–2011 reported 94 live births from 62 women with fVII deficiency. The median fVII activity was 5.5%. Hemostatic prophylaxis was used in 32% of deliveries. Without prophylaxis, 40 vaginal deliveries and 16 cesarean sections were completed. The odds of receiving prophylaxis were 2.9 times higher in women undergoing cesarean section compared to vaginal delivery. Post-partum hemorrhage occurred in 10% of deliveries with prophylaxis and 13% of deliveries without prophylaxis. The fVII level did not significantly differ between women who did and did not receive prophylaxis.

Conclusion—We present the only systematic review of the management of pregnancy in fVII deficient women. No difference in post-partum hemorrhage was seen in deliveries with and

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Author Contributions

Lisa Baumann Kreuziger completed the literature search, analysis, primary manuscript writing, and revisions. Colleen Morton assisted with data abstraction and content review and revisions. Mark Reding initiated the project and completed content review and revisions.

without prophylaxis. Therefore we recommend that rfVIIa be available in the case of hemorrhage or surgical intervention, but not as mandatory prophylaxis.

Introduction

Factor VII (fVII) deficiency is a rare congenital bleeding disorder that affects 1:500,000 people.[1] Heterozygotes for fVII gene mutations typically have fVII activity levels between 20–60%, whereas homozygotes are expected to have levels <10%, although fVII levels vary based on the genetic mutation.[1] fVII activity level and bleeding tendency do not completely correlate as patients with similar activity levels have variable bleeding tendencies.[2] Additionally, symptomatic heterozygotes have been described.[1] Therefore, it is difficult to predict which patients may need prophylactic replacement of fVII prior to hemostatic challenges.

The type of prophylaxis used in fVII deficient patients has changed over time and depends on product availability.[3] Because of the volume required and risk of viral transmission with fresh frozen plasma (FFP) and the limited availability of fVII concentrate based on country, recombinant factor VIIa (rfVIIa) is the most widely used hemostatic prophylaxis agent.[3] rfVIIa is expensive; using 15–30 mcg/kg can cost thousands of dollars per dose.[4] Thrombotic events have been reported in people with fVII deficiency and hemophilia after use of rfVIIa.[3] Spontaneous deep vein thrombosis and pulmonary embolisms have been also reported in patients with fVII deficiency.[5] Additionally, venous thromboembolism will occur in 1:1000–1:2000 pregnancies. [6] Despite the thrombotic risks, prophylaxis is recommended by many authors for deliveries in fVII deficient women with low fVII levels. [7][8] Previous reviews have used limited cases on which to base recommendations.[8][9] We performed a systematic review of the literature to define the management, hemorrhagic and thrombotic complications of pregnant woman with fVII deficiency.

Materials and Methods

Comprehensive medical databases were searched using the terms “factor VII deficiency” and “pregnancy” or “surgery.” Our search yielded articles from PubMed (n=364), MEDLINE (n=143), CINAHL (n=11), Academic Search Premier (n=39), Cochrane Library (n=2), Web of Science (n=209), and Scopus (n=337). Abstracts from 426 articles were reviewed after 679 duplicates were excluded (Figure 1). References from relevant articles were also assessed yielding an additional 20 articles. Articles were excluded based upon animal studies, another disease, not pregnancy management in FVII deficiency, review only, combined defect, non-English article without abstract, and no fVII level. The remaining 34 articles, 4 abstracts, and 3 institutional cases were reviewed for mode of delivery, type of hemostatic prophylaxis, thrombotic prophylaxis, hemorrhagic and thrombotic complications. Baseline Factor VII levels were recorded. A bleeding history was considered positive if previous menorrhagia, epistaxis, post-traumatic or post-surgical bleeding was reported. Post-partum hemorrhage was defined as >500 ml blood loss with vaginal delivery or >1000 ml blood loss with cesarean section if given.[10] If blood loss was not reported, women were not considered to have hemorrhaged if the authors wrote that no complications occurred or only had minimal bleeding. This study was deemed exempt by the Institutional Review Boards of the University of Minnesota and the Health Partners Research Foundation, St. Paul, MN.

Statistical analysis was completed using JMP 9.0 (SAS Institute Inc., Cary, NC). Categorical outcomes and predictors were compared using Chi-square or two-tailed Fisher’s exact test, as appropriate. fVII levels were compared across groups using Wilcoxon Rank Sum test.

Results

Reports of 94 live births from 62 women with fVII deficiency were published between 1953 and 2011 (Table 1). The median fVII activity of the women was 5.5% (range 0.5–49%). Seventy-six percent of women had levels $\geq 10\%$ and 82% had fVII levels $\geq 20\%$. Maternal bleeding history was available in 68% of deliveries and fVII level was similar in patients with and without a bleeding history (median 2.5% vs. 3.0%, $p=0.24$). With the limitations of missing data, the similar fVII levels suggest a lack of complete correlation between fVII level and bleeding tendency.

Hemostatic prophylaxis was used in 30 deliveries (32%). rfVIIa was administered in 17 deliveries in reports from the US, Europe and Asia published from 1998–2011. FFP was used in 6 deliveries reported from 1979–2011, and plasma-derived fVII concentrate was administered in 6 deliveries reported in 1998–2000. One delivery used both fVII concentrate and FFP. Of the deliveries with prophylaxis, 13 were vaginal, 15 were cesarean section and 2 did not report the mode of delivery (Figure 2). Prophylaxis was used in 25% (13 of 53) of vaginal deliveries, whereas 48% (15 of 31) cesarean sections had prophylaxis. Of the women with reported mode of delivery, the odds of receiving prophylaxis were 2.9 times higher in women undergoing cesarean section compared to women who had vaginal deliveries {OR 2.9 (95% CI: 1.1–7.4)}. Of the women who underwent cesarean section with prophylaxis, 87% used rfVIIa and only one delivery each occurred with FFP or combined FFP and fVII concentrate. rfVIIa was used in 31%, FFP in 31%, and fVII concentrate in 38% of reported vaginal deliveries. Prophylaxis was used in 28% of patients with a bleeding history and 22% of patients without a bleeding history ($p=0.6$). Without prophylaxis, 40 vaginal deliveries and 16 cesarean sections were completed (Figure 2). The fVII level did not significantly differ between women who did and did not receive prophylaxis (Median with prophylaxis 4.4% vs 7% without prophylaxis, $p=0.3$). The median fVII level of women who underwent cesarean section without prophylaxis was significantly higher at 12.3% (range 0.5–49, IQR 3.5–40) compared to women who underwent vaginal delivery without prophylaxis (median 6.5%, range 0.5–49, IQR 1.6–9.9; Wilcoxon $p=0.03$). Of the 11 women undergoing cesarean section without prophylaxis, bleeding history was positive in 5 women, negative in 3 women and not-reported in 3 women. Of the 6 women undergoing cesarean without prophylaxis whose fVII levels were $<10\%$, two did not have a bleeding history and four had a history of menorrhagia. Overall prophylaxis was used preferentially in women undergoing cesarean section, but was not influenced by fVII level or bleeding history.

All but three case reports noted if bleeding complications occurred at delivery and authors were contacted for clarification. Post-partum hemorrhage occurred in 13% of deliveries without prophylaxis and 10% of deliveries with prophylaxis ($p=0.7$). Of the women who hemorrhaged with prophylaxis, two received rfVIIa and one received FFP. All of the hemorrhages on prophylaxis occurred after a cesarean section with estimated blood loss averaging 1400 ml (range 1200–1600). The dose of rfVIIa that was associated with hemorrhage was not reported. Median fVII level was similar in patients with hemorrhage at 1.3% (range 0.5–36%) and without hemorrhage at 4.9% (range 0.5–49%; $p=0.2$). No post-partum hemorrhages occurred in the 18 women without a preceding bleeding history. Of women with a bleeding history, only 18% experienced hemorrhage at delivery (8/44 women). Eleven of 16 caesarean sections without prophylaxis did not have associated hemorrhage and 4 deliveries did not report bleeding outcome. The one reported post-cesarean hemorrhage occurred in a woman with a fVII level of $<0.1\%$ with a history of menorrhagia, spontaneous hematomas, and hemarthrosis. Overall, equivalent rates of post-partum hemorrhage occurred in women irrespective of the use of prophylaxis.

The use of thromboprophylaxis was under-reported in the literature. Of the 94 deliveries, 2 deliveries reported use of thromboprophylaxis.[11, 12] We did not use thromboprophylaxis in our institutional cases. The only reported thrombotic episode was a portal vein thrombosis of undetermined age that was diagnosed in a woman 6 months post-partum. She had not received hemostatic prophylaxis at delivery.[13] Analysis of the risk of thrombosis and utility of thromboprophylaxis in fVII deficient women is limited due to lack of information in published reports.

Discussion

We present the only current systematic review of the management of pregnancy in fVII deficient women. A majority of reported patients had severe deficiency with levels < 10%. Prophylaxis was used in only a third of reported deliveries. Mode of delivery influenced the use of prophylaxis, whereas fVII level and bleeding history did not. Hemorrhage rates were equivalent between women who did and did not receive prophylaxis. Additionally, no post-partum hemorrhages were reported in women who lacked a bleeding history. Therefore, prophylaxis should not be considered mandatory for delivery in all women with factor VII deficiency.

Cesarean section is a surgical procedure, however, and prophylactic use of rfVIIa or fVII concentrate should be considered. Our institutional cases underwent vaginal delivery without prophylaxis, but we planned to use rfVIIa if cesarean section was necessary. Eleven women underwent 16 cesarean sections in the literature without prophylaxis, five of which did not have bleeding outcomes reported. [13–17][18, 19] The women who underwent cesarean section without prophylaxis had higher fVII levels compared to women who underwent vaginal delivery without prophylaxis. Presence of bleeding history could not be used as a distinguishing factor as only 1 of 5 women with a bleeding history hemorrhaged after cesarean section without prophylaxis. Given the limited number of cesarean sections in the literature with reported bleeding outcomes, safety of cesarean section without prophylaxis cannot be ensured.

In congruence with previous reports[2], fVII level did not predict bleeding in this series. In women where bleeding history was reported, fVII levels did not differ between women with and without bleeding history. Furthermore, the fVII levels were equivalent in women who did and did not experience postpartum hemorrhage. The lack of correlation between fVII level and bleeding phenotype may in part be due to the variability in reported fVII level depending on the laboratory reagent used and standardized laboratory criteria have not been established.[20][21] Additionally, women with the same genotype can have inconstant bleeding patterns. Dr. Mariani and the International Factor VII Deficiency Study Group sequenced 313 patients with fVII deficiency and found that bleeding phenotype varied from asymptomatic to severe bleeding in patients with the most common mutations.[2] In general bleeding tendency increased as fVII level decreased, but overlap in fVII level could be seen between the bleeding categories and cutoff values of clinical bleeding could not be determined.[2] The lack of correlation between fVII level and bleeding tendency provides the largest challenge in determining a patient's risk of hemorrhage.

Despite some authors' recommendation to use prophylaxis in women with a bleeding history[7, 8], similar rates of prophylaxis were seen in women with and without a bleeding history in our series. However, only 2/3 of women had information on bleeding history available. The information bias may have influenced the results. However, equal numbers of women were missing information in the prophylaxis and non-prophylaxis group and given the case reports about a bleeding disorder, authors would be more likely to note a history of

bleeding if one was present. Therefore, the risk of systematic misclassification based on bleeding history is low.

Given that a systematic review is limited to the information presented in the literature, there are several weaknesses of the current report. Publication bias is possible as patients managed without intervention or complications might be less likely to be reported in the literature. However, fVII deficiency is a rare disease requiring specialized management and several of the reports were of women without complications. When prophylaxis was used, dosing of rFVIIa varied between 20–60 mcg/kg [11, 22] and fVII concentrate altered between 40 IU/kg to fixed dosing based on vial size. [23, 24] The lack of consistency in dosing does not allow for firm recommendations to be made in the situation that prophylaxis is desired. However, a dose of 15–30 mcg/kg rFVIIa is recommended for use in surgery and bleeding episodes and would be reasonable. [3] Lastly, very few case reports mentioned if thromboprophylaxis was used. Additionally, as only one case report described a thrombotic complication, the risk of thrombosis cannot be estimated with this series. Hopefully data from the International Registry on Congenital Factor VII deficiency [3], FVII Deficiency Treatment Registry [3], or the American Thrombosis & Hemostasis Network database (<http://www.athn.org/>) might give more accurate information on thrombosis risk.

Conclusion

We present the only current systematic review of the literature on management of pregnancy in women with fVII deficiency. As hemorrhage rates were equivalent in women with and without prophylaxis, use of hemostatic prophylaxis should not be considered mandatory but part of an individualized discussion taking into consideration response to previous hemostatic challenges and mode of delivery. Hemostatic agents should be readily available in case of hemorrhage or need for surgical intervention.

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Figure 1.
Systematic review strategy.

Figure 2. Mode of delivery in Factor VII deficient women with and without prophylaxis. Deliveries represented as percent of the total deliveries within the prophylaxis category. Chi-square test compares prophylaxis to non-prophylaxis group.

Table 1

Reported Delivery outcomes in women with Factor VII Deficiency. Papers are listed by first author last name.

	Date	Deliveries (# of women)	Mode of Delivery		Factor VII level Median (range)	Bleeding history (# of women)	Prophylaxis	Post-partum hemorrhage (# of deliveries)
			Vaginal	Cesarean				
Baumann Kreuziger	2013	3 (3)	3	0	<1 (<1-3)	3/3	None	0/3
Benlakhail[18]	2011	4 (4)	0	4	7 (<1-15)	3/4	None	1/4
Comes[11]	2011	1 (1)	0	1	8.0	1/1	rtVIIa	0/1
Kolucki[25]	2011	1 (1)	1	0	6.0	0/1	FFP	0/1
Aynaözlu[26]	2010	1 (1)	0	1	1.6	1/1	rtVIIa	0/1
Klovaite[13]	2010	2 (1)	0	2	27.0	1/1	None	NR
Mandhyan[27]	2010	1 (1)	0	1	<1	1/1	rtVIIa	0/1
Zaidi[12]	2010	1 (1)	0	1	2.4	1/1	FFP + rVII	0/1
Chi[28]	2009	3 (3)	0	3	36 (30-40)	NR	rtVIIa	1/3
Landau[16]	2009	2 (1)	0	2	43	NR	None	NR
Vijapurkar[29]	2009	1 (1)	NR	NR	7.0	NR	FFP	NR
Grolami[30]	2006	8 (4)	8	0	9.75 (9-11)	1/4	None	0/8
Kulkarni[15]	2006	12 (6)	6	6	34.5 (7-49)	NR	rtVIIa (4/12)	1/12
O'Rourke[31]	2006	2 (1)	0	2	<1	NR	rtVIIa	1/2
Pehlivanov[22]	2004	1 (1)	1	0	2.0	1/1	rtVIIa	0/1
Eskandari[32]	2002	1 (1)	1	0	1.0	0/1	rtVIIa	0/1
Giansily-Blaizot[14]	2002	8 (5)	6	2	3 (<1-7)	4/5	None	2/8
De Leo[24]	2000	1 (1)	1	0	<5	0/1	fVII	0/1
Jiménez-Yuste[33]	2000	1 (1)	0	1	4.8	1/1	rtVIIa	0/1
Mariani[34]	1999	1 (1)	1	0	<5	NR	rtVIIa	0/1
Rizk[35]	1999	3 (1)	3	0	<5	0/1	FFP (1/3)	0/3
Soni[36]	1999	1 (1)	NR	NR	4	NR	fVII	0/1
Muleo[37]	1998	1 (1)	0	1	6	1/1	rtVIIa	0/1
Hayat[38]	1998	1 (1)	0	1	5	1/1	rtVIIa	0/1
Iannello[19]	1998	1 (1)	0	1	3	0/1	None	0/1

	Date	Deliveries (# of women)	Mode of Delivery		Factor VII level Median (range)	Bleeding history (# of women)	Prophylaxis	Post-partum hemorrhage (# of deliveries)
			Vaginal	Cesarean				
Signet[39]	1998	2 (2)	2	0	3 and 7	1/2	None	1/2
Cohen[40]	1995	1 (1)	1	0	6	1/1	fVII	0/1
Robertson[23]	1992	4 (2)	4	0	1.3 and 1.7	2/2	fVII (2/4)	2/4
Fadel[41]	1989	2 (2)	2	0	9 and 11	NR	FFP (1/2)	0/2
Pardo[42]	1987	2 (1)	NR	NR	35	0/1	None	0/2
Sakiyama[43]	1988	1 (1)	1	0	3.2	NR	fVII	0/1
Braun[44]	1979	2 (2)	2	0	<1	2/2	FFP (1/2)	0/2
Seligsohn[17]	1970	4 (1)	2	2	9.5	0/1	None	0/4
Heikinheimo[45]	1969	3 (1)	3	0	<5	1/1	None	0/3
Hall[46]	1964	1 (1)	1	0	2.9	1/1	None	0/1
Dische[47]	1959	2 (1)	2	0	<2	1/1	None	2/2
Voss[48]	1959	3 (1)	NR	NR	3.5	1/1	None	0/3
Quick[49]	1955	2 (1)	2	0	14	1/1	None	0/2
Owren[50]	1953	3 (1)	NR	NR	2.5	1/1	None	0/3

NR=Not reported, rFVIIa=recombinant factor VIIa, fVII=factor VII concentrate, FFP=fresh frozen plasma