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Barriers and challenges faced by women with congenital bleeding disorders in Europe: Results of a patient survey conducted by the European Haemophilia Consortium

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Introduction: Historically, issues faced by women with bleeding disorders (WBD) have been underestimated. While advances in genetic testing have resulted in improvements, significant challenges remain in the initial recognition of abnormal bleeding and referral of WBD.

Methods: The European Haemophilia Consortium (EHC) developed a questionnaire for WBD to provide insights into the barriers and challenges faced by WBD in Europe.

Results: In total, 709 WBD responded to the survey from 32 countries, predominantly from western European countries (94%). A delay in ascertaining the diagnosis of a congenital bleeding disorders (CBD) remains, with a median age at diagnosis of 16 years. The presence of family history is strongly associated with a lower median age at diagnosis of 6 years. WBD reported significant disease impact on their day-to-day life, most evident for the rarer CBD. The bleeding symptom of biggest impact on daily life is heavy menstrual bleeding (HMB), reported by 55% of women. Importantly, 25% of WBD reports that their condition severely impacted their decision to have or has prevented them from having children. Respondents registered with Haemophilia Treatment Centres (HTC) are 2.2 times more likely to receive treatment compared to WBD in other hospital services.

Conclusion: Improved education for both patients and healthcare providers is essential to improve time to diagnosis, access to treatment and psychosocial supports for WBD in Europe.

KEYWORDS
access, quality of life, women with bleeding disorders

1 | INTRODUCTION

Historically, issues experienced by women with bleeding disorders (WBD) and their impact on their health and quality of life (QoL) have been underestimated. While advances in genetic testing have led to some improvements in diagnosis of WBD, significant challenges remain in the initial recognition of abnormal bleeding and referral of WBD.[1]

The historical perspective of haemophilia as the archetypal bleeding disorder, affecting only males, casts a long shadow over the evaluation of WBD. Congenital bleeding disorders (CBD) encompass a broad array of platelet function and coagulation factor defects, many of which affect both males and females equally, yet women still struggle to gain recognition from physicians that they have pathological bleeding.[2] Compared to their male counterparts, WBD not only experience general bleeding symptoms, but also undergo a

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monthly haemostatic challenge of menstruation in addition to the increased risk of excessive bleeding associated with childbirth.

For WBD, it is well established that heavy menstrual bleeding (HMB) is the most common bleeding symptom, reported by up to 80% of these women in cohort studies.[3-5] HMB may result in impairment of daily activities, decreased QoL, time off work/school, missed employment opportunities and iron deficiency.[6,7] Studies have shown that WBD are more likely to undergo a hysterectomy and have this procedure at a younger age than healthy controls.[5,8,9]

Treatment of WBD should aim to improve QoL, prevent unnecessary surgical intervention, hospitalization and mortality. The management of gynaecological bleeding problems may be improved by increased awareness and recognition of abnormal bleeding symptoms, prompt and accurate diagnosis, and a multidisciplinary approach to patient care.[6]

In determining the overall impact of bleeding in WBD, the focus is often on clinical outcome data such as haemoglobin, ferritin or generic QoL scores. However, these parameters may fail to capture the true impact of the condition for WBD.[1] The aim of this survey, carried out by the European Haemophilia Consortium (EHC), was to provide the patient voice of their lived experiences with CBD and provide insights into the barriers and challenges faced by WBD in Europe.

2 | METHODS

Between October 2017 and January 2018, the EHC developed a questionnaire for WBD and disseminated it to WBD through the Haemophilia Treatment Centres (HTCs), or the national member organizations (NMO) of the EHC. All WBD were eligible to respond, and the survey was available in English, French, Dutch, German, Swedish, Danish, Norwegian, Macedonian and Russian. All responses were collected using SurveyMonkey Inc (San Mateo, CA).

In the results analysis, haemophilia carriers were classified as those with and without mild haemophilia, according to plasma factor VIII or factor IX levels: (<40 IU/dL or >40 IU/dL), respectively, platelet function disorders (PFD), von Willebrand Disease (VWD) or other factor deficiency (OFD).

Respondents were asked how their bleeding disorder impacted their physical activities (eg sports or gardening), romantic and social life, active life (eg work or school) and reproductive life (ability or willingness to have children). A Likert scale was used to assess the impact on physical, romantic and active life (1 = no impact, 5 = severe impact) and reproductive life, (1 = no impact on their ability or willingness to have children, 5 = preventing them from being able to have or from making the decision to have children). Qualitative data were collected through open questions, about both the most frequently experienced bleeding symptom and the symptoms that had the largest impact on their daily life. They were subsequently divided using cluster analysis on whether they experienced epistaxis, bruising, HMB, oral cavity bleeding, surgical bleeding or joint or muscle bleeding. There were no specific questions relating to the experiences of women and pregnancy in this survey. Respondents were asked where their initial contact/referral and final diagnoses took place, the age at which their diagnosis was made and the type of treatment they were receiving for their bleeding disorder from a list of possible treatments. The complete survey is available on request from the EHC Women's committee.

Statistical analysis was performed with STATA version 13 (StataCorp). Standard *t* tests (parametric), Mann-Whitney test (non-parametric) and chi-squared analyses were used as appropriate, and logistic regression analysis was used to determine odds ratio (OR) with confidence intervals (CI) and adjust for age. Mean Likert scales were compared to assess whether the presence of a positive family history influenced the disease impact assessments.

3 | RESULTS

In total, 709 WBD responded from 32 countries, predominantly from western European countries (94.4%). The highest proportion of respondents were from the Netherlands (29.5%, n = 209), with 23.4% (n = 167) from France, 14% (n = 99) from the United Kingdom, 8% (n = 57) from Denmark and 7% (n = 61) from Germany. The majority of the respondents were adults, with only 27 (3.8%) aged <18 years. Most respondents (56.1%) were aged between 19 and 45 years, 29.9% between 46 and 60 years and 72 (10.2%) were over 60 years old.

In total, 24% of the respondents were carriers of haemophilia A and B with normal levels (>40 IU/dL), 27% were carriers with low levels (<40 IU/dL), 28% VWD, 9% PFD, 5% OFD (Factors V, XI, XIII), 4.4% combined deficiencies and 2.5% had the diagnosis of an unknown CBD (Table 1).

TABLE 1 Summary of WBD respondents

Disorder	n	Per cent
Carrier <40 IU/dL	193	27.22
Carrier >40 IU/dL	169	23.84
VWD	198	27.93
Type 1	62	
Type 2	58	
Type 3	30	
Unknown	48	
PFD	63	8.89
Other factor deficiency (OFD; FV, FXI, FXIII)	37	5.22
Unknown	18	2.54
Combined deficiencies	31	4.37

TABLE 2 Mean age of diagnosis of women with bleeding disorders by family history (*P* value—Mann-Whitney *U* test)

	No family history			Family history			
	n	Median	IQR	N	Median	IQR	*P*
Carrier >40 IU/dL	36	19	4-30	35	5	0-26	0.04
VWD	89	17	3-29	16	1	0-25	0.02
Carrier <40 IU/dL	51	17	7-31	43	16	0-28	0.11
PFD	21	16	7-30				
OFD	18	8	1-17	3	3	0-45	
Unknown	3	28	28-40				
Combined deficiencies	14	20	8-39	2	32.5	26-39	

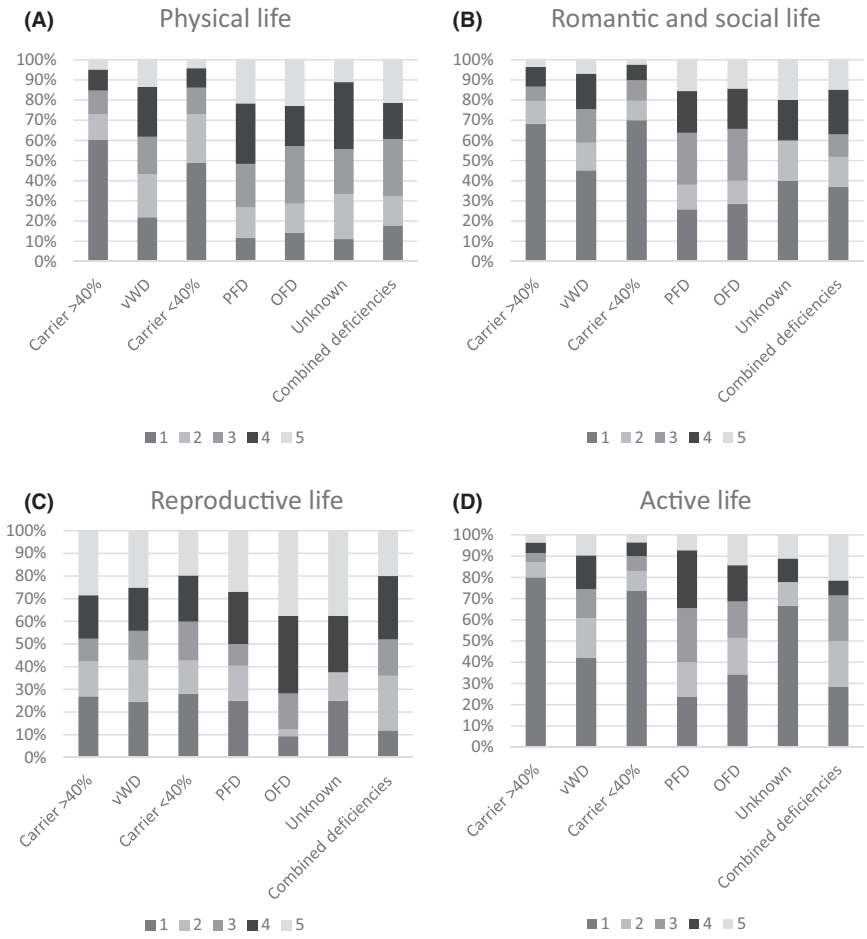

FIGURE 1 Responses of women and bleeding disorder when asked about (A) physical, (B) romantic and social, (C) active and (D) reproductive lives using a Likert Scale (1, no impact—5 severe impact)

3.1 | Age of diagnosis

The median reported age at diagnosis was 16 (IQR 2-28) years, however strongly dependent on the family history with a significantly lower median age (6 years, IQR 0-26) in those with a family history compared to those without (17 years, IQR 5-28, $P < 0.01$). A family history of a known bleeding disorder was also strongly associated with an early diagnosis before the age of 5 years (odds ratio 3.7, 95% CI 2.4-5.9, adjusted for age). In the different subgroups of WBD, both carriers of haemophilia (median age at diagnosis 5 vs 19 years, $P = 0.04$) and women with VWD (median age at diagnosis 1 vs 17, $P = 0.02$) were diagnosed significantly earlier if they had a known family history. More severe types of VWD were diagnosed earlier compared to less severe types, with an earlier age at diagnosis in females with type 3 VWD (median = 1 years, IQR 0-2), in comparison with type 2 VWD (median 19.3 years IQR 3-27, $P < 0.01$, compared to type 3) or type 1 VWD patients (median 25 years IQR 13-33, $P < 0.01$, compared to type 3). The age difference at diagnosis between VWD types 1 and 2 was not statically significant ($P = 0.35$). For women with other bleeding disorders, the subgroups were too small for accurate analysis (Table 2).

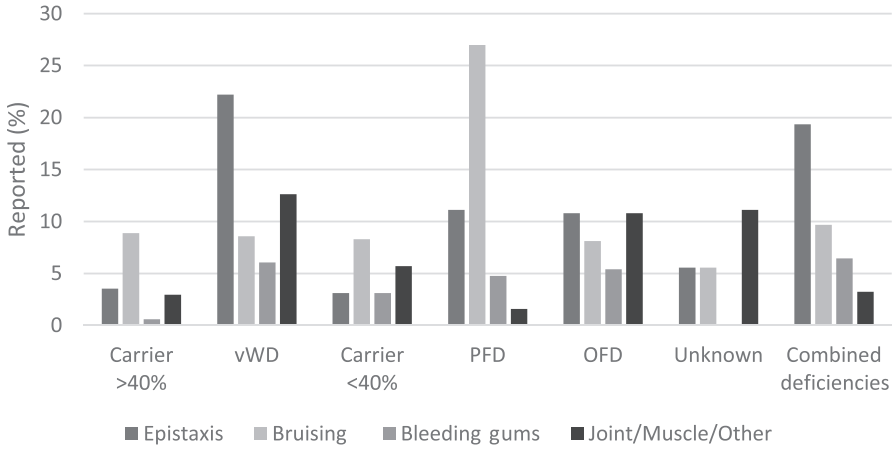

FIGURE 2 Day-to-day bleeding symptoms that affect women with bleeding disorders excluding menstruation

TABLE 3 Reported treatment use in women with bleeding disorders

	Replacement products[a]		DDAVP		Tranexamic acid		Hormonal options (eg contraception pill)	
	n	%	n	%	n	%	n	%
Carrier >40 IU/dL	24	14	9	5	14	9	10	12
vWD	79	40	44	22	68	45	36	44
Carrier <40 IU/dL	43	22	21	11	30	20	14	17
PFD	14	22	8	13	16	11	12	15
OFD	5	14	1	3	8	5	3	4
Unknown	2	11	1	6	3	2	2	2
Combined deficiencies	18	58	7	23	12	8	4	5

[a]Replacement products include plasma-derived or recombinant FVIII/FIX, vWF only plasma-derived products, FVIII containing vWF products, prothrombin complex concentrates, platelet concentrates fresh frozen plasma and cryoprecipitate.

3.2 | Impact of CBDs on personal life and activities

In three domains of daily life (physical, romantic and active) as shown in Figure 1, the greatest impact was reported by women with PFD and OFD compared to the other bleeding disorders. Carriers of haemophilia reported the lowest impact across these domains, with no significant difference between carriers with factor levels <40 IU/dL or >40 IU/dL. Reproductive life was the only domain in which no statistically significant differences were identified between different bleeding disorders. Surprisingly, 25% of the women reported that their condition has had a severe impact on their decision or has prevented them from having children, ranging from 19% in haemophilia carriers with levels <40 IU/dL to 37.5% in those with OFD and combined deficiencies.

Women with no known family history reported significantly greater impact on physical life ($P < 0.01$), social and romantic life ($P < 0.01$) and active life ($P < 0.01$) compared to those with a family history of a bleeding disorder. There was no difference seen in their responses relating reproductive life.

Some of the more impactful qualitative reports included the following: "I have to plan bathroom times between appointments." "Up to 40 changes a day," using "a bandage and tampon at the same time," "always have a change of clothes at work" and "regularly change sanitary protection and 20 minutes later has blood flowing down my legs."

3.3 | Bleeding symptoms

Heavy menstrual bleeding was the most commonly reported symptom (55%); 10% also reported anaemia and/or fatigue. HMB was reported most by women with VWD (70%) but widely reported by WBD across all CBDs (41% of carriers >40 IU/dL, 51% of carriers <40 IU/dL, 54% with OFD, 57% platelet disorder).

Other common symptoms were epistaxis (10% overall), bruising (10% overall) and oral cavity bleeding (4% overall) (Figure 2). Highest rates of epistaxis were reported in women with VWD (22%), significantly more often, compared to carriers of haemophilia (3%). Bruising was reported most by the women with PFD (27%). Joint and muscle bleeds were reported most by women with VWD (13%) and with OFD (11%). Carriers of haemophilia also reported joint and muscle bleeding, experienced by 6% of those with low levels and 3% of women with normal levels. The nature of this bleeding (traumatic

TABLE 4 Respondents indication of initial contact/referral and final diagnosis service

	HTC		Hospital service		Paediatrician		General practitioner		Gynaecology		Otorhinolaryngology		Dentist		Other	
	Initial contact/ Referral	Final diagnosis	Initial contact/ Referral	Final diagnosis	Initial contact/ Referral	Final diagnosis	Initial contact/ Referral	Final diagnosis	Initial contact/ Referral	Final diagnosis	Initial contact/ Referral	Final diagnosis	Initial contact/ Referral	Final diagnosis	Initial contact/ Referral	Final diagnosis
Carrier >40%																
n	52	93	15	22	12	3	8	1	3	1	1	0	2	0	28	12
%	42.98	70.45	12.4	16.67	9.92	2.27	6.61	0.76	2.48	0.76	0.83	0	1.65	0	23.14	9.09
vWD																
n	34	103	50	50	15	6	23	3	14	1	4	0	6	0	27	9
%	19.65	59.88	28.9	29.07	8.67	3.49	13.29	1.74	8.09	0.58	2.31	0	3.47	0	15.61	5.23
Carrier <40%																
n	69	122	23	30	21	5	15	1	6	0	6	0	2	0	20	8
%	42.59	73.49	14.2	18.07	12.96	3.01	9.26	0.6	3.7	0	3.7	0	1.23	0	12.35	4.82
PFD																
n	3	24	14	31	1	0	20	0	2	0	1	0	1	0	15	4
%	5.26	40.68	24.56	52.54	1.75	0	35.09	0	3.51	0	1.75	0	1.75	0	26.32	6.78
OFD																
n	3	16	9	14	2	3	6	0	4	0	5	1	2	1	3	0
%	8.82	45.71	26.47	40	5.88	8.57	17.65	0	11.76	0	14.71	2.86	5.88	2.86	8.82	0
Unknown																
n	1	5	3	4	0	0	3	0	4	1	0	0	0	0	0	0
%	9.09	50	27.27	40	0	0	27.27	0	36.36	10	0	0	0	0	0	0
Combined deficiencies																
n	5	19	5	4	2	0	1	0	5	1	2	0	0	0	7	1
%	18.52	76	18.52	16	7.41	0	3.7	0	18.52	4	7.41	0	0	0	25.93	4

or spontaneous) and whether it was verified by clinical assessment was not assessed in this survey.

3.4 | Access to treatment

When surveyed on the use and access to treatments such as tranexamic acid, hormonal treatment, replacement products (including plasma-derived or recombinant factor concentrates, platelet concentrates and fresh frozen plasma) and desmopressin (DDAVP), 317 (45%) respondents report the use of some form of treatment (Table 3). Of those who reported receiving treatment, 55% received one form of treatment, 30% used two treatments, 13% three treatment forms and only 2% had used all four different treatments. A strong treatment correlation was observed between respondents who were receiving treatment and involvement of a HTC in their care (odds ratio 2.2, 95% CI 1.7-3.1). Overall, the odds ratio for receiving treatment when linked with a HTC was 1.6 (1.1-2.2) for replacement products, 2.01 (1.3-3.4) for DDAVP, 2.7 (1.8-4.0) for tranexamic acid, 2.2, (1.4-3.7) for hormonal options and 2.21 (1.4-3.7) for ≥2 treatments.

3.5 | Diagnosis location

Overall, 29% of initial contact/referral took place in a HTC and 20% in general haematology. Other clinical areas of initial contact/referral diagnosis included general practice (13%), paediatrics (9%), gynaecology (7%), otorhinolaryngology (3%) or from their dentist (2%; Table 4).

About 17% of respondents underwent early screening due to a preceding family history. Women who were carriers of haemophilia were more likely to be diagnosed in a HTC in comparison with other conditions ($P < 0.01$), with 43% of carriers identified through a HTC, compared to 20% of those with VWD, 18% of those with combined deficiencies, 9% of OFD and 5% of PFD.

A final diagnosis was received by most WBD through a HTC (64%), followed by a general haematology hospital service (26%) or through a paediatrician (3%). There was a difference across disorders, with 72% of carriers, 60% of those with VWD and 76% of those with combined deficiencies received their diagnosis in a HTC, compared to less than half of the women with PFD or OFD (41% and 46%, respectively).

4 | DISCUSSION

In this study, we report the results of the largest European survey on 709 WBD to date, from 32 European countries. These results highlight several important and ongoing challenges for WBD in Europe: spanning the lifecycle of a chronic illness from diagnosis, to treatment and the impact of symptoms on daily and reproductive life. The study emphasized several significant impacts on the QoL for WBD; however, further research in the area of WBD is necessary to enable healthcare providers to treat, understand and support this cohort of patients effectively.

A number of limitations of the current study are worth noting. Despite 32 countries being represented and included in the study, the sample is largely a western population, the findings of this survey may not be representative for all WBD in Europe and further data in Eastern European countries would be of interest to highlight any medical, cultural or psychosocial differences. Secondly, for patients reporting a diagnosis of a platelet function disorder and OFD, the current study did not have the opportunity for a more in-depth analysis of specific concerns or issues regarding these subtype diagnoses. Further research, with a more clearly defined diagnoses, may highlight significant differences or challenges between disorders.

The study offered an insight into the complex experience WBD face. Firstly, delays in both recognition of abnormal bleeding and ascertaining a diagnosis of a CBD remain, with a median age at diagnosis of 16 years. The presence of family history, increasing both patient and physician awareness for a CBD improved the median age at diagnosis to 6 years. WBD reported significant disease impact on their day-to-day life, most evident for the rarer CBDs.

The bleeding symptom of biggest impact on daily life was HMB, reported by 55% of women. HMB resulted in anaemia and severe fatigue in many cases. The qualitative responses indicate the major impact on QoL experienced by some women with reporting of such statements as “I would have to use a bandage and tampon at the same time and keep a change of clothes at work” or “I would have to plan bathroom times between appointments (at work).” These reports correspond to several other studies which identify HMB leading to anaemia, pain and tiredness, all of which have a significant negative effect on the respondents ability to work and their QoL.[10,11] These data suggest that major steps have to be taken in the near future to improve treatment of HMB in WBD.

From the other bleeding symptoms, affecting the respondents’ epistaxis and bruising were reported to have a significant impact; although for epistaxis, this impact was episodic. Bruising was a more persistent problem with respondents reporting feeling self-conscious due to the location and size of their bruising. A further interesting and unexplained finding was reporting of joint and muscle bleeding by a small number of carriers of haemophilia. This is a key point for further research to assess whether these women are truly at an increased risk of joint and muscle bleeding or it is their perception explaining joint/muscle pain.

Strikingly, 1 in 4 WBD reported their condition severely impacted their decision to have or has prevented them from having children independent of the underlying CBD. For those patients without a family history, there was an even greater impact, possibly due to delayed diagnosis and/or potentially less access to treatment. Possibly, women face social stigma of an inherited bleeding disorder that prevents them from getting married or having a family and could be a subject in future surveys. As many WBDs use hormonal treatments to control their HMB, this may have impact on their decision to have children as it will require change in treatment.[3] Poorly controlled HMB may also influence the decision to undergo early hysterectomy, prematurely limiting reproductive choices. A recent study highlighted the value placed

by WBD in proactive engagement from healthcare providers in the treatment of HMB.[12] This is reiterated in our survey which highlights the negative impact of CBD on reproductive choices, underscoring the necessity of education and counselling by experienced health care workers and support networks for WBD, to improve prenatal support.

The finding that HTC involvement is more frequent in women with a positive family history indicates not only an increased awareness of diagnostic pathways in these women, but also the trust developed with HTCs based on previous familial interactions. More importantly, WBD are almost twice as likely to receive some form of treatment if registered with a HTC and twice as likely to report access to two or more medication forms for their condition, compared to WBD who do not attend a HTC. This may be due to more severe CBD cases known and treated at HTC but demonstrates the obvious benefits for WBD who are treated through a HTC compared to a general hospital-based service. Hence, it is vital that NMOs and HTCs consider how to actively engage with WBD to provide the much needed multidisciplinary support proactively.[12-14]

5 | CONCLUSION

The present survey improves the understanding of experiences of WBD with CBD represented by the EHC. The results will help to define areas for future focus to enhance support and services for WBDs across Europe. This survey exposes important deficits in patient information for WBDs regarding management of HMB and reproductive choices and in the clinical management of the rarer CBDs. Improved education for both patients and healthcare providers is essential to improve the diagnosis and management for WBD in Europe.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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REFERENCES

1. Hermans C, Kulkarni R. Women with bleeding disorders. *Haemophilia*. 2018;24(9):29-36.
2. Paroskie A, Oso O, Almassi B, DeBaun MR, Sidonio RF. Both hemophilia health care providers and hemophilia a carriers report that carriers have excessive bleeding. *J Pediatr Hematol Oncol*. 2014;36(4):e224-e230.
3. Byams VR, Kouides PA, Kulkarni R, et al. Surveillance of female patients with inherited bleeding disorders in United States Haemophilia Treatment Centres. *Haemophilia*. 2011;17(Suppl. 1):6-13.
4. Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA. Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. *Haemophilia*. 1999;5(1):40-48.
5. Lavin M, Aguila S, Dalton N, et al. Significant gynecological bleeding in women with low von Willebrand factor levels. *Blood Adv*. 2018;2(14):1784-1791.
6. Kulkarni R. Improving care and treatment options for women and girls with bleeding disorders. *Eur J Haematol*. 2015;95(5):2-10.
7. Von Mackensen S. Quality of life in women with bleeding disorders. *Haemophilia*. 2011;17(Suppl. 1):33-37.
8. James AH. Women and bleeding disorders. *Haemophilia*. 2010;16(Suppl. 5):160-167.
9. de Wee E, Knol HM, Mauser-Bunschoten EP, et al. Gynaecological and obstetric bleeding in moderate and severe von Willebrand disease. *Thromb Haemost*. 2011;106(11):885-892.
10. Winikoff R, Amesse C, James A, Lee C, Pollard D. The role of haemophilia treatment centres in providing services to women with bleeding disorders. *Haemophilia*. 2004;10(s4):196-204.
11. Kadir RA, Edlund M, Von Mackensen S. The impact of menstrual disorders on quality of life in women with inherited bleeding disorders. *Haemophilia*. 2010;16(5):832-839.
12. Eising HP, Sanders YV, de Meris J, Leebeek F, Meijer K. Women prefer proactive support from providers for treatment of heavy menstrual bleeding: a qualitative study in adult women with moderate or severe Von Willebrand disease. *Haemophilia*. 2018;24(6):950-956.
13. Zia A, Lau M, Journeycake J, et al. Developing a multidisciplinary Young Women's Blood Disorders Program: a single-centre approach with guidance for other centres. *Haemophilia*. 2016;22(2):199-207.
14. Khair K, Holland M, Pollard D. The experience of girls and young women with inherited bleeding disorders. *Haemophilia*. 2013;19(5):e276-e281.

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