sciendo

Bleeding disorders in girls and women: setting the scene

Naja Skouw-Rasmussen, Michelle Lavin, Minette van der Ven

The prevalence and impact of bleeding disorders in women is not sufficiently acknowledged, with the organisation of care traditionally biased towards boys and men with haemophilia. In 2017, the European Haemophilia Consortium surveyed women with bleeding disorders, national member organisations (NMOs) and treatment centres to assess the impact of bleeding disorders in women in four domains: physical activity, active life, romantic and social life, and reproductive life. Most women had von Willebrand disease (VWD) or described themselves as a carrier. All reported a negative impact on physical activity, active life and romantic and social life. Up to 70% of women in all groups reported that their bleeding disorder had a significant impact on their ability or willingness to have children, or prevented it. Heavy menstrual bleeding was reported as the having the most significant impact on daily life. Women face barriers to diagnosis and care, including difficulty obtaining a referral and lack of knowledge among general practitioners and gynaecologists. While bleeding disorders share many symptoms, including bleeding after minor injury and trauma, the link between heavy menstrual bleeding and a bleeding disorder often goes unrecognised and its severity is underestimated. Screening is not offered to all eligible women despite the availability of long-established management guidelines; clinical tools to estimate severity may be unreliable. Failure to recognise a bleeding disorder in a woman is a multifactorial problem that is partly due to cultural reluctance to discuss menstruation. Public awareness campaigns are seeking to correct this, and many NMOs involve women in their initiatives and provide women-centred activities. However, a transformation in diagnosis is needed to shift the focus of treatment centres beyond boys and men with haemophilia, and to acknowledge the prevalence and severity of bleeding disorders in women.

NAJA SKOUW-RASMUSSEN
Member of the Steering Committee and Chair of the of the Women and Bleeding Disorders Committee, European Haemophilia Consortium, Denmark

MICHELLE LAVIN
Consultant Haematologist, National Coagulation Centre, St James's Hospital, Dublin, Ireland; Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland

MINETTE VAN DER VEN
Vice-President, Finance, European Haemophilia Consortium, The Netherlands

PROCEEDINGS OF THE THE FIRST EUROPEAN CONFERENCE ON WOMEN AND BLEEDING DISORDERS

Keywords: *Women, von Willebrand disease, diagnosis, menstrual bleeding, haemophilia*

WOMEN AND BLEEDING DISORDERS IN EUROPE: RESULTS FROM THE EHC SURVEY

Every year, the European Haemophilia Consortium (EHC) conducts an annual survey of its membership about a topic associated with bleeding disorders. In 2017, the survey focused on women – a group within the bleeding disorders community that has historically been overlooked and

about whom there is little scientific information – to determine how the EHC can act to raise awareness.

The survey addressed four key areas:

- Identifying women with bleeding disorders
- Access to diagnosis
- Access to treatment and care
- Availability of psychosocial support.

The survey was issued to three groups: women with a bleeding disorder (or spouse) (WBD); EHC national member organisations (NMOs); and haemophilia treatment centres in Europe (HTCs). The survey form was designed to be short and easy to complete to maximise the response rate. It could be completed online or in hard copy, and was available in English, Russian, French, Danish, Norwegian, Swedish, Dutch, Macedonian, Latvian and German. The survey was carried out between October 2017 and January 2018. A report on the responses of WBD to the survey has been published [1].

Table 1A. Types of bleeding disorders among survey respondents [1]

BLEEDING DISORDER	NUMBER	PERCENTAGE
Von Willebrand disease	198	27.93%
Carrier <40%*	193	27.22%
Carrier >40%*	169	23.84%
Platelet disorders	63	8.89%
Other factor deficiencies	37	5.22%
Combined deficiencies	31	4.37%
Unknown	18	2.54%

* 74% Haemophilia A; 26% Haemophilia B

Table 1B. VWD type among survey respondents (N=198) [1]

VWD	PERCENTAGE
Type 1	40%
Type 2	40%
Type 3	19%
Type 1/2	1%

Table 1C. Platelet disorders among survey respondents (N=63) [1]

PLATELET DISORDER	PERCENTAGE
Immune thrombocytopenic purpura (ITP)	40%
Glanzmann thrombasthenia	8%
Storage pool deficiency	6%
Thrombocytopathy	3%
Bernard-Soulier syndrome	2%
Unknown	41%

Women with bleeding disorders

Responses were received from 709 WBD, of whom 94% were from Western Europe, 4% from Central Europe and 2% from Eastern Europe. Over half (56%) were aged 19–45, 30% were 46–60 years old, 10% were aged 61 or older, and 4% were under 18. The largest groups were women with von Willebrand disease (VWD, 28%) or who described themselves as carriers of haemophilia with factor level >40% (24%) or <40% (27%); approximately 9% of respondents had a platelet disorder (see Tables 1A – 1C).

The impact of a bleeding disorder was assessed in four domains:

- Physical activity, such as sports or gardening
- Active life, including education or professional training
- Romantic and social life, including relationships, friendships and social activities
- Reproductive life, including ability or willingness to have children.

All WBD reported a negative impact on physical activity, active life and romantic and social life; this was greater among women with a platelet disorder, other factor deficiencies or unknown diagnosis. Between 40% and 70% of women in all groups reported that their bleeding disorder had a significant impact on their ability or willingness to have children, or prevented it.

The impact of bleeding on daily life ranged from nose bleeds (higher in women with VWD or a combined factor deficiency) and bruising (highest in those with a platelet disorder), but heavy menstrual bleeding had the greatest impact of all. This was reported by 70% of women with VWD, 41-44% among carriers with >40% factor activity or unknown diagnosis, and 51-61% of other women. Statements from individuals show that the impact of menstruation was substantial (Table 2), and many reported having to plan their lives around their menstruation.

Women reported that their initial diagnoses were made in various settings but most frequently in secondary care; the diagnosis was confirmed in an HTC in 64%. This suggests that women consult a range of healthcare professionals before they receive a clear diagnosis, highlighting the need to raise awareness in all care settings.

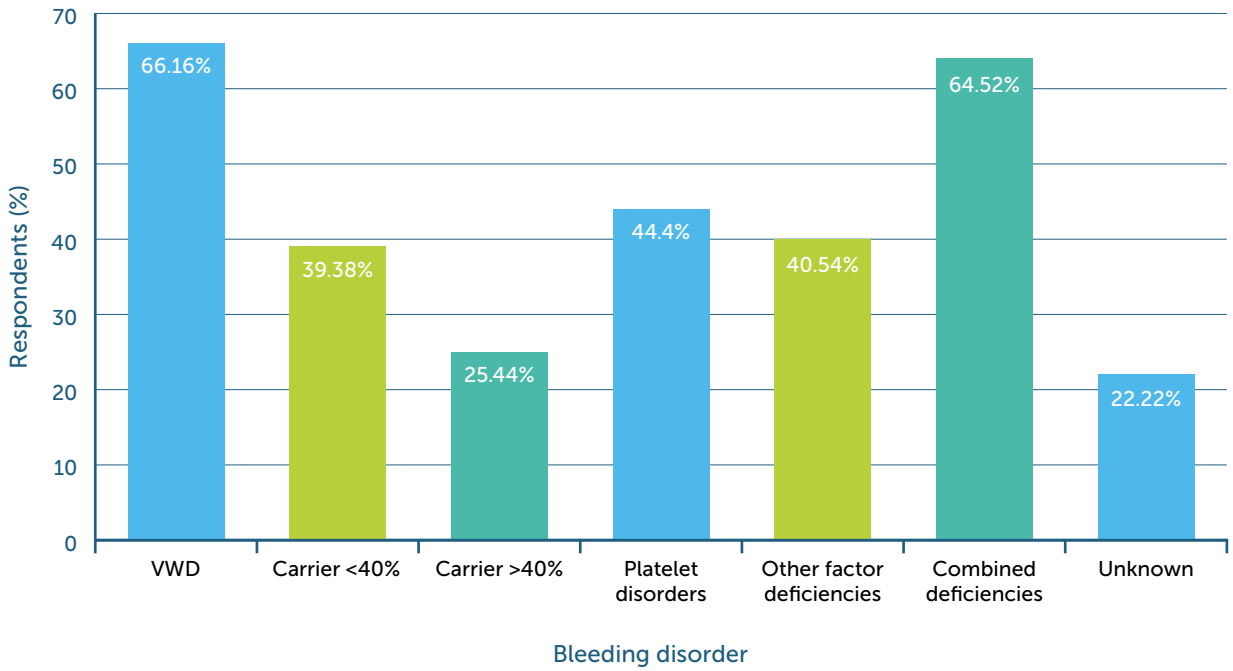
The diagnosis of a bleeding disorder was made relatively late for many women (mean age 16.7 years +/-15 years), but was lower for women with VWD and carrier status when a family history was known. Just over one third of women were diagnosed before age five, and this was strongly associated with a family

J Haem Pract 2019; 6(2). doi: 10.17225/jhp00138

Table 2. Personal statements about the impact of menstruation

- "Needed blood transfusion of two units - as a result missed out on a new career"
- "Have to plan bathroom times between appointments. Up to 40 changes a day"
- Had "a bandage and tampon at the same time" and "had a change of clothes at work"
- Severe bleeding for "over ten years resulting hysterectomy at 38"
- "I would regularly change sanitary protection and 20 minutes later have blood flowing down my legs"
- "I would have to stay in bed for three to four days a month because I was so exhausted"

Figure 1. Proportions of women receiving treatment for their bleeding disorder [1]



history after adjustment for age at the time of the survey (odds ratio 3.7, 95%CI 2.4-5.9).

The proportion of women who reported having treatment for their bleeding disorder was highest among those with VWD or a combined deficiency (Figure 1). Less than half of women with a platelet disorder or other factor deficiency were receiving treatment, suggesting the possibility of few options for these conditions. Despite the high impact of heavy menstrual bleeding, there was relatively low usage of hormone treatments, which raises questions about their effectiveness and tolerability.

HTCs and NMOs

Responses were received from 15 HTCs. Eight reported that they followed national or international guidelines on diagnosis and treatment, though there was little consistency between centres. Some countries did not have a patient registry and lacked data on epidemiology.

Comments from respondents show that the barriers to accessing appropriate diagnosis and care included difficulty obtaining a referral; lack of knowledge and coordination among general practitioners and gynaecologists; and having few national experts and few centres where a firm diagnosis can be made. Some primary care doctors were unaware that a bleeding disorder is a risk factor for post-partum haemorrhage or menorrhagia.

Twenty-seven NMOs responded to the survey. They reported a wide range of membership numbers, which was highest in the UK (2,819) and Belgium (1,580), and lowest (≤20) in Albania, the Czech Republic, Israel, Montenegro and Serbia. The proportion of members who were women tended to increase with membership number, ranging from about half in Belgium, Latvia and

the UK, to ≤12% in Israel, the Czech Republic, Portugal, Serbia and Albania. Fourteen NMOs were able to provide complete information about the distribution of types of bleeding disorder among women.

NMOs provide a lot of care and support to their members. Women are represented at board level or in working groups in 23 countries; there are activities targeted specifically at women in 19 countries, and NMOs in 21 countries have published information about WBD.

Summary

HTCs provide good quality care but, overall, there is room for improvement where WBD are concerned – in particular, delays in diagnosis and referral must be addressed and access to treatment should be improved. The EHC survey shows that WBD are impaired by their bleeding disorder. The impact on daily life is significant for all disorders, but the problems are greatest among women with platelet disorders, other factor deficiencies or undiagnosed disorders. The management of menstruation is the issue most frequently reported, but this is a topic that many have difficulty talking about openly. There is much to be done to raise awareness and increase knowledge among healthcare professionals, but it is also important that WBD themselves share their experiences. Women's voices need to be heard and a significant improvement in support, treatment and management is required.

AN OVERVIEW OF RARE BLEEDING DISORDERS IN WOMEN

Bleeding disorders may be caused by a deficiency or poor function of clotting factors (e.g. haemophilia A and B, von Willebrand disease) or platelets (e.g. Glanzmann's thrombasthenia, Bernard-Soulier syndrome). However, there are also bleeding disorders of unknown cause that share many symptoms associated with excessive bleeding, including spontaneous events such as nosebleeds, bruising, bleeding after teeth brushing and from cuts and minor wounds; heavy menstrual bleeding; bleeding in the kidney, gastrointestinal tract, brain and joints; and bleeding associated with childbirth, dental extraction and surgery.

Bleeding disorders in women and men

Expert care is traditionally provided via haemophilia treatment centres. This term is increasingly being seen as problematic as it does not acknowledge the large number of people with bleeding disorders other than haemophilia, and does nothing to challenge the traditional view that bleeding disorders are clinically significant only in men. This is a view perpetuated by medical education that concentrates on haemophilia as a recessive X-linked disorder, which can leave healthcare professionals poorly informed about bleeding disorders in women.

Women with haemophilia are usually described as 'carriers', which suggests they are not affected by their bleeding disorder. Some have factor levels <40%, which is equivalent to the category of mild haemophilia in men. However, using factor level as a surrogate for bleeding risk is misleading: women with higher factor levels may also experience excessive bleeding. In this context, initiatives such as the Twitter hashtag *#womenbleedtoo* are an important step in raising awareness.

Regardless of type of bleeding disorder and factor level, WBD differ from men in one very important respect: heavy menstrual bleeding is particularly troublesome. The medical definition of heavy menstrual bleeding (losing ≥80ml in each period, having periods that last longer than seven days, or both) does not fully capture its impact on women who have to change tampons or pads every two hours or more frequently, and experience clots or flooding. They may lose so much blood that they have iron deficiency anaemia, which causes fatigue and impairs concentration. It is not sufficiently recognised that bleeding disorders are common among women who seek help for heavy menstrual bleeding. The disorders and their treatments affect the personal health of women and affect their families; they determine choices about having children; they affect employment and social activities. Bleeding disorders in women are – or should be - a major public health concern.

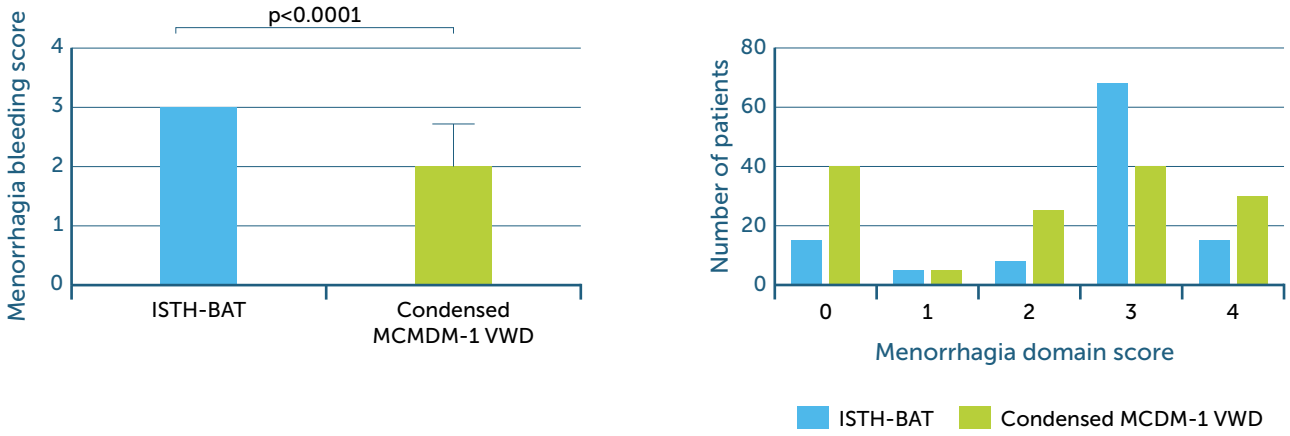
Under-recognition of bleeding disorders in women

Based on prevalence estimates of heavy menstrual bleeding and bleeding disorders, there are perhaps 4–5 million women with a bleeding disorder in Europe. The World Federation of Hemophilia (WFH) Annual Global Survey shows that the average prevalence of diagnosed haemophilia (defined as a factor level <40%) is about 1 in 10,000 [2]. In the 2017 WFH report, women account for only 3% of cases of haemophilia A and 5% of cases of haemophilia B. Women with a factor level of <40% are classed as carriers and excluded from the report. Bearing in mind that every male with haemophilia has a mother, this grossly underestimates the number of people with a bleeding disorder.

The proportion of cases of other bleeding disorders who are women ranges from approximately 40% to 60%. However, these figures are also misleading: the

J Haem Pract 2019; 6(2). doi: 10.17225/jhp00138

Figure 2. Menorrhagia bleeding scores in women with low von Willebrand factor [4]



The bar charts compare the ISTH-BAT and Condensed MCMDM-1 VWD menorrhagia-domain scores among women in the Low von Willebrand in Ireland Cohort (LoVIC) study, based on identical clinical information [4]

prevalence of von Willebrand disease, for example, should be approximately ten times greater than that of haemophilia, but the data suggest the figure is less than half. Defining the severity of a bleeding disorder by factor level alone, rather than considering the personal impact of bleeds, seriously underestimates the burden of symptoms.

Screening for bleeding disorders in women

One reason for the under-diagnosis of bleeding disorders in women is that they are often missed during screening. A recent US retrospective study identified 23,888 post-pubertal girls and adolescents with heavy menstrual bleeding (986 with severe heavy menstrual bleeding, defined as heavy menstrual bleeding plus an inpatient stay for menstrual bleeding, iron deficiency anaemia or blood transfusion) in a health insurance claims database [3]. Although screening guidelines were well established at the time, only 8% of all girls and 16% of those with heavy menstrual bleeding were screened for von Willebrand disease.

Failure to recognise a bleeding disorder is a multifactorial problem. Women with heavy menstrual bleeding may believe their experience is normal, particularly if it is shared by their mother or sisters. There is still a cultural taboo about discussing menstruation in both developed and developing economies, meaning that it is not easy for individuals to discover what is 'normal'. A number of campaigns are now aiming to raise awareness among physicians (RRED: Recognise Refer Educate Diagnose) and women (Let's Talk. Period; Period. The Menstrual Movement; Know Your Flow). The new campaign #721 aims to explain what constitutes 'normal' or 'heavy' bleeding based on bleeding criteria (bleeding for >7 days, changing pads or tampons every two hours, blood clots the size of a one euro coin).

When a woman is offered screening for a bleeding disorder, there is scope for misdiagnosis. Primary care physicians often rely on a simple coagulation test, which is insensitive to most common bleeding disorders. Treatment centres use either the Condensed Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD (Condensed MCMDM-1 VWD) or the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) – but these tests produce different bleeding scores from the same clinical information (Figure 2) [4]. The ISTH-BAT utilises mainly clinical criteria, but the MCMDM-1 VWD score requires a medical consultation. The consultation element, however, has been shown to be an unreliable marker: in the Low von Willebrand in Ireland Cohort study, only 60% of women reported heavy menstrual bleeding to a physician prior to study entry, but 89% self-reported heavy menstrual bleeding, with 70% noting heavy periods since their first period and 39% recording >2 days off work or school per year as a result [4]. The study also showed that those who reported heavy menstrual bleeding to a physician were not diagnosed with von Willebrand disease earlier than those who did not (34.2 vs 33.4 years, p=0.07). Furthermore, 37% of women had seen two or more specialists before they were offered screening.

These data suggest that women are effectively bleeding their way to a diagnosis and show the importance of patient-focused questions in the assessment. There is clear guidance on when a bleeding disorder should be considered: the American College of Obstetricians and Gynecologists states this possibility should suspected in a teenager with heavy menstrual bleeding since her first period, and heavy menstrual bleeding associated with bleeding when challenged (e.g. by surgery, dental procedure or childbirth), or more than one of bruising, nosebleeds, gum bleeding and a family history [5].

Lived experience

Healthcare professionals are trained to diagnose bleeding disorders according to the presentation of classic symptoms, but not every person with the same diagnosis has the same bleeding experience. A transformation in diagnosis in women is needed, based around refocusing the efforts of treatment centres beyond boys and men with haemophilia to acknowledge the prevalence and severity of bleeding disorders in women. Assessment should include patient-focused rather than procedural questions, and the participation of women in research should be increased by redesigning methodologies. There is a need to raise public awareness of bleeding disorders via campaigns that include social media, so that women more readily recognise heavy bleeding and obtain an earlier diagnosis.

Developments in gene therapy are drawing scientific and public attention and also funding to solving a problem in men. Further thought should be given to devoting appropriate resources to women with bleeding disorders.

DISCUSSION

Questions from the audience focused largely on what more NMOs could do to support women and how to improve the services of treatment centres.

It was felt that WBD should act through NMOs to encourage treatment centres to improve their services for women and audit their performance. While adult services are accustomed to the challenges of heavy menstrual bleeding, the onset of menstruation occurs in the paediatric setting. Centres should develop a pathway specifically to address menstruation, ensuring that girls have access to information appropriate to their individual case in a setting that is comfortable (i.e. not with their father). This would enable girls to recognise the differences between 'normal' and heavy periods. Menstruation might also be a pertinent issue to address as part of the transition process, provided it begins at a young age. NMOs could meet this demand through youth clinics, subject to resources being available.

In general, menstruation is a subject that needs to be discussed much more openly, and peer-to-peer discussion should be encouraged through youth committees and clinics. Schools may offer another channel of communication, though it is unclear whether it would be better to approach local institutions individually or seek to influence policy at a national level. Girls need the opportunity to learn about menstruation in a non-embarrassing setting, but parents should also be made aware of the significance of heavy periods. At the same time, the needs of WBD should not be forgotten in efforts to improve information for young people. NMOs should share ideas and resources to avoid duplication.

KEY MESSAGES

- Bleeding disorders have a negative impact on all domains of life, including planning a family
- Heavy menstrual bleeding has the greatest impact on daily life and is experienced by most women with a bleeding disorder
- The average age at diagnosis of a bleeding disorder is 16-17
- Women face barriers to accessing timely diagnosis and treatment
- The prevalence and impact of bleeding disorders on women is not fully recognised
- Women with heavy menstrual bleeding are not adequately screened for bleeding disorders
- There is a cultural reluctance to talk about menstruation and a need to raise public awareness
- Treatment for boys and men with severe and moderate haemophilia is now much more effective, and there is scope for treatment centres to further develop their focus on those inherited bleeding disorders that affect males and females in equal numbers, but where women have more risk of regular and debilitating bleeding due to menstruation and childbirth.

J Haem Pract 2019; 6(2). doi: 10.17225/jhp00138

Finally, as many bleeding disorders are familial, the opportunity to offer screening to symptomatic relatives should not be missed. Women at risk by virtue of being a relative of a patient with a bleeding disorder may be identified from patient registries, provided data protection obligations are met – it must also be borne in mind that some people may not want to have a diagnosis. In Ireland, relatives of people registered with a bleeding disorder are able to self-refer to a centre for assessment, avoiding the barriers associated with the traditional referral pathway.

Girls with heavy menstrual bleeding due to a bleeding disorder have difficult decisions to address: they need to consider the benefits and drawbacks of hormonal treatment, and they will also become aware of the possible impact of their condition and its treatment on fertility. NMOs are in a strong position to provide the information and support that will help them find the answers.

ACKNOWLEDGEMENTS

Writing support was provided by Steve Chaplin, Haemnet.

The authors have advised no interests that might be perceived as posing a conflict or bias.

This article does not contain any studies involving human participants or animals performed by any of the authors.

ORCID

Michelle Lavin https://orcid.org/0000-0003-2999-4216

REFERENCES

1. Noone D, Skouw-Rasmussen N, Lavin M, van Galen KPM, Kadir RA. Barriers and challenges faced by women with congenital bleeding disorders in Europe: Results of a patient survey conducted by the European Haemophilia Consortium. *Haemophilia* 2019; 25(3): 468-74. doi: 10.1111/hae.13722.
2. World Federation of Hemophilia. WFH Annual Report 2017. Available from *http://www1.wfh.org/publications/files/pdf-1696.pdf* (accessed 29 May 2019).
3. Jacobson AE, Vesely SK, Koch T, Campbell K, O'Brien SH. Patterns of von Willebrand disease screening in girls and adolescents with heavy menstrual bleeding. *Obstet Gynecol* 2018; 131: 1121-29. doi: 10.1097/AOG.0000000000002620.
4. Lavin M, Aguila S, Dalton N, *et al.* Significant gynecological bleeding in women with low von Willebrand factor levels. *Blood Adv* 2018; 2: 1784-91. doi: 10.1182/bloodadvances.2018017418.
5. Committee on Adolescent Health Care, Committee on Gynecologic Practice, American College of Obstetrics and Gynecology. Committee Opinion No. 580: von Willebrand disease in women. *Obstet Gynecol* 2013; 122: 1368-73. doi: 10.1097/01.AOG.0000438961.38979.19.

HOW TO CITE THIS ARTICLE

Skouw-Rasmussen N, Lavin M, van der Ven M. Bleeding disorders in girls and women: setting the scene. Proceedings of the First European Conference on Women and Bleeding Disorders. *J Haem Pract* 2019; 6(2): 3-9. https://doi.org/10.17225/jhp00138