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Women and girls with inherited bleeding disorders: Focus on haemophilia carriers and heavy menstrual bleeding

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Abstract

Raising awareness and improving recognition, accurate classification, and enhanced access to new treatments represent current key challenges for carriers of haemophilia. Women and girls carrying genes for haemophilia often experience significant bleeding and/or low factor levels. The bleeding associated with female haemophilia is frequently overlooked, has a weak correlation with factor levels, and manifests differently than in males, with heavy menstrual bleeding being a predominant symptom. Recent changes in terminology now allow the diagnosis of haemophilia in females with low factor levels and differentiate between symptomatic and asymptomatic carriers of the gene.

Observations from real-world experiences and limited clinical trial data have highlighted the positive impact of various new haemophilia treatments for women and girls with clotting factor deficiencies. There is an urgent need for initiatives that increase their access to these treatments and encourage well-designed clinical trials focusing on female-specific outcomes.

In women with inherited bleeding disorders, early recognition and optimal management of heavy menstrual bleeding are crucial. However, treatment options and guidance from high-quality clinical trials are currently insufficient. Menstrual health assessment should be a regular part of monitoring women and girls with inherited bleeding disorders throughout their lives, emphasizing the importance of gathering data to improve future management.

KEYWORDS
carrier, haemophilia, heavy menstrual bleeding, innovation, women and girls

1 | NEW HAEMOPHILIA CARRIER CLASSIFICATION: HOW DO WE ADAPT OUR CARE PATHWAYS?

1.1 | Introduction

Haemophilia A and B are rare X-linked inherited bleeding disorders (IBDs) that result from deficiencies in coagulation factor VIII (FVIII) or factor IX (FIX). Until recently, the inheritance pattern of haemophilia had been mischaracterized as a 'recessive' X-linked pattern in which males are affected but females are not.[1–4] For the purpose of this article, the term female is inclusive of any person or group of people with relevant biological female sex characteristics.

The longstanding failure to recognize that females can also have bleeding and haemophilia has led to underestimations of the prevalence of haemophilia and expectations of clinical manifestations informed by the male experience.[1–4] Meanwhile, there is growing evidence that haemophilia genotype-positive females commonly experience excessive bleeding, delays in diagnosis, undertreatment, and poor quality of life.[1–4]

1.2 | New haemophilia nomenclature

In 2021, a joint communication from the Scientific and Standardization Committees (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) put forward a new nomenclature for females in haemophilia.[1] Under this new classification, the diagnosis of haemophilia in females is defined by the same baseline FVIII/FIX level (hereafter called factor level) as in males: factor levels < 1 IU/dL define severe haemophilia, factor levels of 1–5 IU/dL define moderate haemophilia, and factor levels > 5 and < 40 IU/dL define mild haemophilia.[5] The ISTH joint SSC panel recognized that genotype-positive females can bleed excessively even when factor levels are normal. Therefore, two other categories were created for genotype-positive females with factor levels ≥ 40 IU/dL: females with excessive bleeding are now termed symptomatic carriers, while females who do not have excessive bleeding are termed asymptomatic carriers.[1] More recently, a higher cut-off using a factor level of ≥ 50 IU/dL has been proposed for the diagnosis of symptomatic carriers in addition to genotype and bleeding phenotype females.[2] A cut-off factor level of 50 IU/dL increases access to the diagnosis of haemophilia for more females, but also overlaps with the low end of the factor level normal range and may over-diagnose some who are not at high-risk for bleeding. More evidence is needed to know if a cut-off of either 40 or 50 IU/dL should be used.

1.3 | Factor levels, genetics, and bleeding in females

Females with haemophilia genotypes overall have low factor levels, with median levels about half those of people without haemophilia (60 IU/dL).[1] There is a wide variation in levels in females around this median observed, ranging from < 1 IU/dL to over 200 IU/dL.[1,6] About half of genotype-positive females have clinically significant bleeding. Under the new ISTH SSC nomenclature, 28% of females are expected to have levels < 40 IU/dL and a diagnosis of haemophilia, while more than a quarter of females with normal factor levels will have significant bleeding and meet criteria for symptomatic carrier.[1]

Genetics plays a significant role in low factor levels in females. The FVIII and FIX proteins are encoded by the corresponding *F8* and *F9* genes on the X chromosome. Most males with haemophilia are genetically XY (hemizygous for the X chromosome) and the haemophilia-causing gene variants are completely penetrant because there is only one copy of the gene. On the other hand, most haemophilia-genotype positive females are XX (heterozygous) and have two copies of the *F8* and *F9* genes. Different than in males, females with haemophilia genotypes usually have one gene copy that expresses some normal coagulation factor. However, occasionally haemophilia can be fully penetrant in females, such as in cases of hemizygosity due to large deletions or Turner's syndrome (X0), homozygosity or compound heterozygosity causing two-affected gene copies, or complete X-chromosome inactivation (XCI) leading to silencing of the normal gene.[1,6]

XCI is an epigenetic process which inactivates 'extra' X chromosomes in cells that have more than one X chromosome early in development. The result is a mosaic of somatic cells with one population of cells expressing only maternal X genes and a second population expressing only paternal X genes.[7] If XCI occurs randomly, XCI skewing should be normally distributed with extreme XCI skewing (> 90:10) predicted to occur in 0.01%–2.1% of females.[8] However, skewed XCI can also result from non-stochastic processes, such as heritable variation in XCI control genes, persistence of imprinting, and preferential inactivation of an abnormal X allele.[7] In haemophilia, both random-appearing and heritable skewed XCI have been observed. XCI measures generally correlate with levels but may not predict bleeding in females with borderline or normal levels.[3]

The clinical presentation of symptomatic genotype-positive females is distinct from that of males. In addition to factor levels correlating poorly with bleeding in females,[9,10] the pattern of bleeding is different. Males with haemophilia have bleeding in muscle, soft tissue, and joints and excessive bleeding from invasive procedures or injuries. In females, heavy menstrual bleeding (HMB) is the most common bleeding symptom with other clinically significant bleeding including postpartum hemorrhage, epistaxis, bruising, bleeding with procedures, and joint and muscle bleeding.[2–4] There is limited data directly comparing males and females with the same factor levels, more research is needed. A retrospective study assessed 44 females with mild FVIII or FIX deficiency (levels between 5–50 IU/dL) alongside 77 males with mild haemophilia A or B. The study compared these groups based on clotting factor levels, age, reasons for diagnosis, and treatment approaches. After removing symptoms of bleeding that are specific to one gender, it was found that both haemophilia carriers with plasma factor levels within the mild haemophilia range and males with mild haemophilia exhibit similar bleeding patterns, primarily mucocutaneous and postinjury bleeding. However, haemophilia carriers with clotting factor deficiencies were noted to have distinct characteristics, including a later age of diagnosis, higher average factor levels, and different triggers leading to diagnosis.[11]

1.4 | Prevalence of females at-risk

In order to better resource clinical care and research for female haemophilia, the demographics and healthcare access for females need to be understood. For every male with haemophilia, there should be about 2.7 females at-risk to inherit and 1.6 genotype-positive females.[12] Half of genotype-positive females have clinically significant bleeding, so for every male there should be about 0.8 females with bleeding who warrant clinical care. However, far fewer females than males are seen in centers. For example, in a survey of US Hemophilia Treatment Center (HTC) data from 2012–2020,[13] 23,728 males were seen in HTCs. Only about 18% (n = 3504) of the expected 19,000 females with bleeding were seen at HTCs over the 2012–2020 time period. This missingness impacts many females. The prevalence of males affected by haemophilia at birth is estimated to be 1 in 5000 for

haemophilia A and 1 in 30,000 for haemophilia B[5,14] (or higher[15]). With a global population of 4 billion males and 3.95 billion females, there are over 1 million females predicted to be affected by haemophilia worldwide, of whom most are likely not receiving timely or adequate care.

1.5 | Adapting our care pathways

It is now critical to improve haemophilia education in order to increase the recognition of at-risk females and promote the early and accurate diagnosis including genetic testing, factor level measurements, and a detailed history.[1,6] Early and accurate diagnosis is the first step to accessing health care resources, insurance coverage, and specialty centers. Once a female is diagnosed, recognition of bleeding, prompt treatment, and lifelong prevention are needed throughout the lifespan. Figure 1 shows the ideal timing of testing and management of events unique to females through each life stage.[16,17]

2 | IMPACT OF THERAPEUTIC INNOVATIONS ON WOMEN AND GIRLS WITH HAEMOPHILIA

2.1 | The therapeutic revolution of haemophilia: For women and girls

The development of clotting factor concentrates with prolonged half-lives, allowing for less frequent intravenous injections, subcutaneous hemostatic agents with different modes of action and targets (bispecific antibodies, rebalancing agents), providing constant haemostatic potential unparalleled in the past, and the opportunity for endogenous production (gene therapy), are all evidence of the therapeutic revolution in haemophilia.[18,19] This revolution, however, has so far been primarily male-centric, benefiting mainly boys and men with haemophilia.[20] The observation is that almost exclusively male haemophilia patients with severe haemophilia benefit from these innovations. They are eligible for clinical studies or have access to

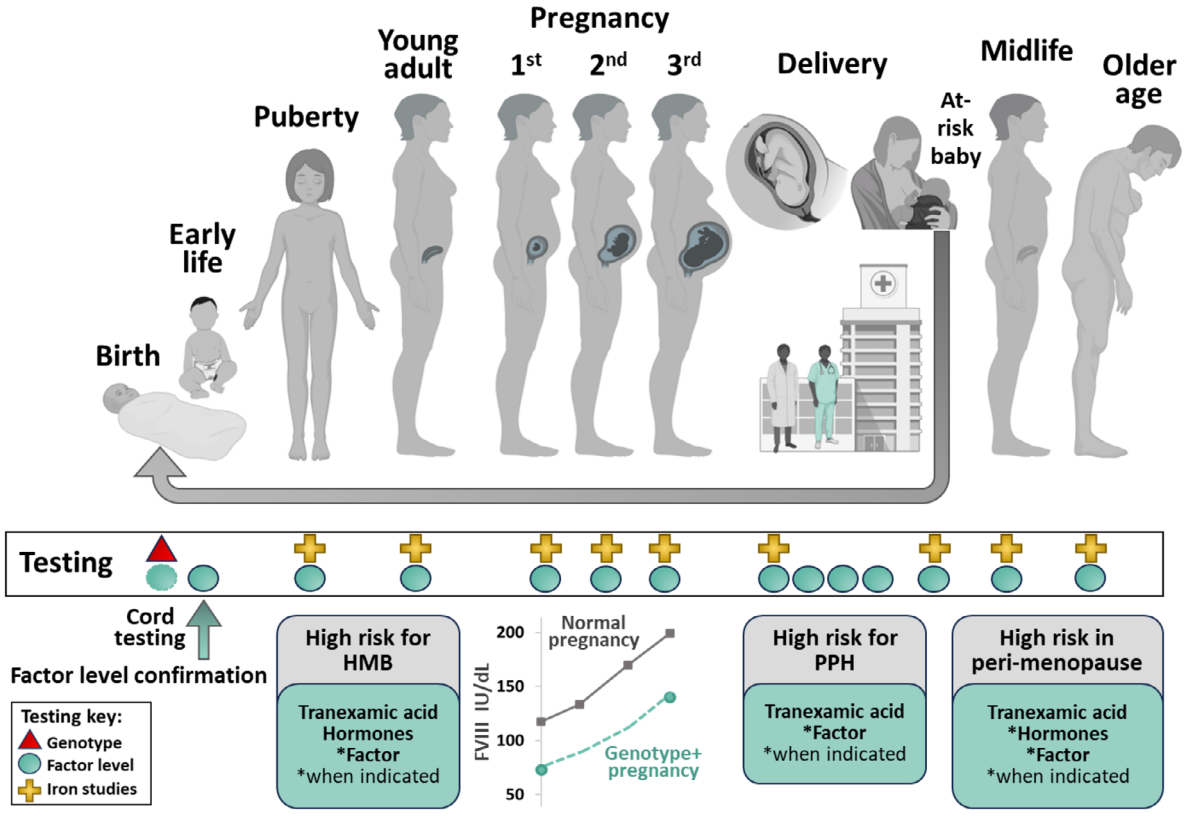

FIGURE 1 Lifespan of a female with a haemophilia-causing genotype. Shown is a schematic of the life stages of a haemophilia genotype-positive female. Below the schematic are timelines for testing and common treatments relevant to female reproductive tract bleeding (colored boxes). Ideally, at-risk females will be identified before birth. Cord blood should be sent for genetic testing and screened for factor level. The factor level baseline should be confirmed in early life after the hemostasis system is mature. If an at-risk female presents later in life, they should have factor levels, genotype, and iron studies tested regardless of age. Factor levels and iron studies should be tested periodically throughout life. Females who menstruate or become pregnant are at high risk for HMB, ovarian hemorrhage, excessive peri-menopausal bleeding, and PPH. Shown under the pregnancy life stage is the median rise in FVIII levels for healthy pregnancy (adapted from data in ref. [16]) and for females with haemophilia genotypes (adapted from data in ref. [17]). FIX levels also generally increase in pregnancy. PPH correlates poorly with third-trimester factor levels[17] and all females should be considered at high risk for PPH, deliver in resourced settings, and receive prophylaxis for PPH with tranexamic acid and, if indicated, factor replacement with close laboratory monitoring. Life stage figures were created with BioRender.com. HMB, heavy menstrual bleeding; PPH, postpartum hemorrhage.

innovative treatments registered by official agencies and financially supported in their geographical area. This prioritization of research towards male patients can largely be explained by the predominance of severe forms of FVIII or FIX deficits in these individuals, whereas female patients are mostly faced with mild deficits and rarely moderate ones.

However, a revolution in haemophilia care is underway. Its scope is enormous and extends far beyond the adoption of new treatments. It involves systematically identifying carriers with FVIII or FIX deficiency as recently reported,[21] recording their bleeding complaints, assessing the physical and psychological impacts of their haemophilia, giving them access to appropriate treatments, including new treatments, and above all, raising awareness in the community about these challenges.

While nearly all male haemophilia patients are known and identified, at least in countries with sufficient resources, and are cared for in multidisciplinary centers, regularly followed up, and rigorously accounted for in registries, this is not the case for women and girls with haemophilia. Their low numbers, even in rigorously maintained national registries such as in the UK (United Kingdom Haemophilia Centre Doctors' Organisation [UKHCDO]) and France (France Coag), clearly demonstrate this.[22,23] Indeed, only 601 female haemophilia patients were registered in the French France–Coag registry in 2021, representing 7% of the total number of patients in this registry. According to the last UKHCDO report, 3381 women and girls with haemophilia were registered, representing 29% of the total number of patients.[22,23] Therefore, it seems essential to be proactive and promote systematic screening of haemophilia carriers, especially those with a FVIII or FIX deficiency. These women should be classified as haemophiliacs, like boys and men with a similar clotting factor severity of deficiency and receive comparable care.

Even though most female patients in the France–Coag and the UKHCDO registries have a mild clotting factor deficiency (96 % in both registries), some suffer from moderate and even severe disease, albeit exceptionally. Mild haemophilia, which predominates among these female patients, should not be trivialized. In addition to bleeding complaints common in both sexes (nosebleeds, bruises, etc.), these women also experience often exacerbated gynecological and obstetrical bleeding due to the FVIII or FIX deficiency.[11] Although the control of bleeding in the reproductive tract is primarily attributed to platelets and von Willebrand factor, the recent finding that emicizumab can alleviate menstrual bleeding suggests a local function for FVIII. However, this remains an area requiring more in-depth investigation.[24] These female patients are also at risk of developing haemophilic arthropathy and disproportionate bleeding during haemostatic challenges.[25]

Although robust demographic data is often lacking, every haemophilia center has several symptomatic female patients. These women should have access to innovative treatments that are currently available to male patients. This statement might be viewed as overly assertive when considering the limited validation of innovative treatments for patients with mild and moderate haemophilia A and B, particularly in females, along with their limited accessibility and high costs. Nonetheless, it underscores the unmet need and the importance of advocacy in making these treatments available to women and girls. Scientific validation in female haemophiliacs is however often lacking. Women and girls with haemophilia are indeed almost systematically excluded from clinical trials, which mainly include male subjects with severe haemophilia, a rare entity in female haemophiliacs. Furthermore, these clinical studies do not include efficacy criteria for gynaecological and obstetric bleeding.

2.2 | Treatment innovations in women and girls: Current data and perspectives

Several recent publications based on real-life data have reported local beneficial experiences with several innovative treatments, including the use of long half-life FIX concentrates and emicizumab in female haemophilia B and A patients, respectively.[26,27] It is also noteworthy that the only clinical study specifically dedicated to moderate and mild haemophilia A patients treated with emicizumab (Haven 6) included three female haemophilia A patients.[24] This study is unique in that it is the only one to date that has incorporated female haemophiliacs treated with an innovative treatment. The follow-up of these patients in that study clearly demonstrated that they also benefit from this treatment, also for gynecological bleeding complaints.

These preliminary and limited data can only encourage the access of female haemophilia patients to innovative treatments, while not neglecting the essential role played by various traditional obstetric and gynecological treatments (such as multiple hormonal therapies, tranexamic acid) and interventions (like endometrial ablation). Even if the efficacy and safety data from studies in male haemophiliacs can probably be extrapolated, specific studies in female haemophiliacs must be welcomed. These studies, currently almost non-existent, must consider a different distribution of haemophilia severity, specific bleeding complaints, particular hemostatic challenges (periods, childbirth), and define their own evaluation criteria. The possibility of transplacental passage of each haemostatic agent and the modalities of appropriate contraception must also be considered. Moreover, the fluctuation of clotting factor levels during pregnancy and the effects of hormonal therapies pose additional complexities. The pharmacokinetics and pharmacodynamics of haemophilia treatments in women and girls remain unexplored. Importantly, protocols will also have to adapt to the personal and family constraints specific to female haemophiliacs.

Most female hemophiliacs with moderate and some with mild FVIII or FIX deficiencies will probably require treatments that normalize haemostasis. In this respect, bispecific antibodies mimicking FVIII, agents acting on physiological inhibitors of coagulation, as well as innovative approaches such as the use of nano-antibodies binding endogenous factors (present in small amounts) to albumin as well as aptamers seem promising.[28,29] Given that various innovative treatments could provide variable and different benefits due to their specific modes of action, several molecules should ideally be evaluated. However, such ambitious initiatives can only materialize with the initiative and will of pharmaceutical partners, healthcare professionals, the involvement of patients and their relatives, and the support of patient associations.

In the immediate future, it seems important to ensure that women and girls with haemophilia are identified without delay, informed about innovative treatments and their advancements, and able to benefit from them. The collection of rigorous clinical data, the creation of specific registries, and the multiplication of information and awareness initiatives can only be encouraged. These initiatives must also permeate countries with limited resources, where access to innovative therapies is gradually developing, currently almost exclusively to the benefit of men.

2.3 | On the way to a better future

The therapeutic revolution among women and young girls with haemophilia is underway. The multiple therapeutic options now available finally offer the possibility to end segregation, repair an injustice, and enable women and young girls with haemophilia to reduce or eliminate the physical and mental consequences of their FVIII or FIX deficiency, irrespectively of their clotting factors levels and bleeding phenotype.

3 | HEAVY MENSTRUAL BLEEDING: FROM MENARCHE TO MENOPAUSE

3.1 | Background

HMB is one of the most commonly experienced haemorrhagic symptoms for women and girls with an IBD and affects more than 80% of individuals at some time during their childbearing years.[30] Definitions for HMB vary, but perhaps the most pragmatic, and patient-centered definition was set by the National Institute for Health and Care Excellence (NICE) in the UK, as: 'excessive menstrual blood loss which interferes with a woman's physical, social, emotional, and/or material quality of life'.[31] HMB is not simply restricted to women and girls with IBD, and reports detail that one in every 20 menstruating women seek medical attention every year for HMB,[31] but the duration and extent of menstrual blood loss is often greater in those with IBD compared to those without.[32] Furthermore, during adolescence, HMB may be the only symptom that a young woman with an IBD may experience. There have been many reports detailing the significant impact that HMB can have on a woman's life. These include both the physical effects, which often relate to iron depletion and iron deficiency anemia, as well as the significant, but often less recognized, effects on quality of life. HMB can cause social anxiety; can lead to avoidance of social, sporting and leisure activities; and can negatively interfere with school and working life.[33,34] It is therefore imperative that we focus our attention on managing this common and often poorly treated condition to positively impact all aspects of our patients' lives.

Three years ago, the European Haemophilia Consortium (EHC) and the European Association for Haemophilia and Allied Disorders (EAHAD) jointly published a report which set out the 10 recommendations they had developed, in close collaboration with patients, to start to address the needs of women and girls with IBD. These are the 'European principles of care for women and girls with IBDs'. The recommendations delineate the breadth of care that all patients with IBD should have access to, across their lifetime, and cover clinical, quality of life, educational and research domains.[35] The seventh principle is to provide 'early recognition and optimal management of HMB'.[35]

3.2 | Challenges to delivering optimal care for HMB

3.2.1 | Changing needs across a lifetime

Menstruation occurs, on average, every 4–5 weeks from the menarche and can continue for up to four decades. The needs of an individual across that time will, naturally, vary widely. For example, a young girl who is pre-menarche will have a different knowledge base, and physiology, to an older individual making it even more important that patients are managed as individuals. Equally importantly, but often overlooked in busy clinics, is that the amount of blood loss a woman experiences each month is not static and HMB can start many years after the menarche. As clinicians, we need to be recognizant of these changing needs and provide care that is flexible and responsive.

Despite this, there are, a handful of times in a patient's life where heavy menstrual blood loss is more likely: at the menarche and in the months immediately afterwards, when anovulatory menstrual cycles are more common; in the postnatal period when menstruation returns; and in the peri-menopausal years. Many clinicians advocate the use of the pictorial blood assessment chart (PBAC), which a patient completes at each cycle, to estimate menstrual blood loss.[36] This, whilst an imperfect measure, can be a very helpful means to monitor fluctuations both across a woman's lifetime but also her response to treatment. Temporally less easy to predict, but still a common cause for HMB, are structural lesions, such as fibroids, which can lead to new-onset or worsening HMB. Our focus, therefore, should be two-fold, both to actively engage with all patients at those life-events more commonly associated with HMB and to encourage patient self-advocacy to contact IBD clinicians if faced with new or changing HMB symptoms. One example of supporting girls with IBD is to develop individual 'menarche management plans' prior to the menarche, and including their guardians/parents, where appropriate.[37] In this way, girls can be encouraged to discuss their expectations, and concerns, and they and their families can be reassured that they will be supported through this event. Similarly, a plan for resumption of the menses can be made in the later stages of pregnancy for those approaching delivery and in a clinic appointment for those approaching their menopause. Treatments will also vary, according to the life-stage of the patient as well as the acceptability of the treatments for individuals (in particular, hormonal therapies), which can add another layer of complexity to management. Again, it is this complexity which emphasizes the importance of an individualized approach.

3.2.2 | Self-advocacy and breaking down barriers

It is not uncommon for patients with IBD to feel that their HMB is 'no worse' than perhaps their mother's or their sibling's and therefore is viewed as nothing 'out of the ordinary'.[38] Education, both for the affected individual and her family members, of what is viewed as a normal volume of menstrual blood loss is therefore vital to empower young women to both recognize that they may have HMB and to allow them to openly discuss their experiences of HMB.

One of the particular barriers to open discussion relates to the often-unspoken shame people can feel around their menstrual cycles. A recent study evaluating 10,000 social media posts on the topic of menstruation in girls and young women (age 13–25 years), found three common themes to their posts: menstrual health, menstrual stigma, and menstrual positivity. Of these themes, there was an overwhelming emphasis across this age group placed on the negative expectations and shame felt around menstruation.[39] IBD clinicians need to be mindful of these barriers: both the familial normalization of HMB, as well as the difficulty many girls and young women feel in openly discussing HMB issues.

3.2.3 | Optimal therapy

It is important to recognize that even when a patient is diagnosed with an IBD and suffers with HMB, this does not guarantee a greater likelihood of successful treatment/reduction of menstrual blood loss. For example, a recent observational study reported that only 68% of an IBD patient cohort gained satisfactory control of their HMB with medical management.[40] It is well recognized that women with HMB and IBD will commonly fail first line, or even second line therapies. Furthermore, high-quality evaluation of specific treatment for IBD and HMB are few. A recent interventional RCT comparing VWF concentrate with TXA for HMB in women with mild and moderate VWD showed no benefit for those in receipt of factor concentrate.[41] Therefore, developing better treatments for control of HMB must continue to be a research focus.

3.3 | How to move forward?

The care of girls and women with HMB and IBD is complex. Treatments are limited (hormonal therapy; antifibrinolytics and desmopressin or factor replacement in more severe cases) and we have little in the way of high quality, longitudinal data, or indeed clinical trial data,[35,41,42] which details how well patients respond to each of these therapies. Future efforts should focus on ensuring that menstrual health is evaluated at every routine clinician-patient contact, during childbearing years, and that we also aim to collect high quality, prospective, patient reported outcomes for girls and women with IBD to direct future management as effectively as possible. In the era of widespread use of social media and digital technologies amongst our patients, collecting self-reported data should be a more realistic goal, and these same technologies should be used for both educating girls and women about normal menses as well as destigmatizing HMB, and encouraging those affected to seek medical support. This will then provide a robust starting point to determine how to direct clinical trials and treatments in the years to come.

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Each author contributed to the writing of a specific section of the manuscript, and all sections were collectively reviewed and approved by all three authors.

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