Women and Hereditary Bleeding Disorders

Alessandra Bosch[1] Dehlia Moussaoui[2] Alessandro Casini[3]

[1] Department of Haematology, University Children's Hospital Zurich, Eleonore Foundation, Zurich, Switzerland
[2] Division of Pediatrics, Obstetrics and Gynecology, University Hospitals of Geneva, Geneva, Switzerland
[3] Division of Angiology and Hemostasis, Faculty of Medicine, University Hospitals of Geneva, Geneva, Switzerland

Address for correspondence Alessandro Casini, MD, Division of Angiology and Hemostasis, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, 1201 Geneva, Switzerland (e-mail: Alessandro.Casini@hcuge.ch).

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Abstract

Hereditary bleeding disorders encompass a range of hemostasis defects that impair the blood coagulation process. Although these disorders affect both men and women, research and clinical management have historically been predominantly focused on male patients, particularly those with hemophilia. Consequently, the impact of these disorders on women has been undervalued and frequently overlooked. The intricate relationship between a woman's tendency to bleed and the various gynecological and obstetric processes gives rise to distinctive health challenges for women with hereditary bleeding disorders. Heavy menstrual bleeding (HMB), excessive bleeding during miscarriages, postpartum hemorrhage, and hemorrhagic ovarian cysts represent some of the most common complications. Despite the high prevalence and significant impact of these symptoms, many women experience delays in diagnosis and treatment, which in turn may result in iron-deficiency anemia, anxiety, influence on reproductive decisions, and a decreased quality of life. This review aims to summarize the distinctive characteristics of hereditary bleeding disorders in women, emphasizing the clinical challenges and hormonal management strategies for HMB.

Keywords

- hemophilia carrier
- von Willebrand disease
- heavy menstrual bleeding
- rare bleeding disorders
- postpartum hemorrhage

Introduction

Hereditary bleeding disorders are a group of hemostasis defects that affect the blood clotting process, resulting in a lifelong predisposition to excessive bleeding.[1] The most prevalent bleeding disorders are von Willebrand disease (VWD) and hemophilia A and B. Other bleeding disorders are referred to as rare bleeding disorders (RBDs).[2] As indicated by the 2022 Annual Global Survey of the World Federation of Hemophilia, individuals affected by RBDs represent 9% of all patients with a bleeding disorder. The complexity of inherited platelet function disorders (IPFDs) has made it challenging to ascertain their prevalence.[3] Another prevalent bleeding disorder is hereditary hemorrhagic telangiectasia (HHT), which is characterized by the presence of mucocutaneous and visceral arteriovenous malformations.[3] The diagnostic work-up includes standard hemostasis assays, measurement of coagulation factors, and platelet function analyses. These tests are now broadly available, allowing for more accurate identification of hereditary bleeding disorders, even in low- and middle-income countries where severe VWD, IPFD, and RBDs are more prevalent.[2]

Women with inherited bleeding disorders experience a variety of bleeding symptoms, before, during, and after their reproductive years (►Fig. 1).[4] In a recent survey conducted by the European Hemophilia Consortium, 709 women with inherited bleeding disorders reported epistaxis, bruising, muscle hematoma, and hemarthroses, depending on the severity of the hemostasis defect.[5] The bleeding phenotype among men and women is similar, although it is more common for women to be referred for issues related to

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Fig. 1 Bleeding symptoms experienced by girls and women with inherited bleeding disorders. *In severe bleeding disorders. **In FXIII deficiency and fibrinogen disorders.

bleeding, and they often require more frequent and more extensive treatment due to the presence of sex-specific bleeding patterns.[6] Indeed, women are exposed to a multitude of bleeding challenges throughout their lives such as heavy menstrual bleeding (HMB) on a monthly basis, excessive bleeding during miscarriages, postpartum hemorrhage, and hemorrhagic ovarian cysts.[7,8] These distinctive health challenges give rise to a notable increase in morbidity, significantly impacting the quality of life.[8,9] A recent systematic literature review has reported that women with a bleeding disorder experience obstacles to accessing care, difficulties living with their disorder, interference with school and work, and poor mental health.[10] Despite the high prevalence and significant impact of these symptoms, many women experience delays in diagnosis and treatment, often due to the misconception that bleeding disorders are predominantly male diseases and due to limited awareness of important HMB indicators by healthcare professionals.[5,11] In addition, women with bleeding disorders are significantly underrepresented, or even excluded, in clinical trials. Currently, only a limited number of trials allow female participants with hemophilia, which has resulted in gaps in data and understanding regarding the management and outcomes of bleeding disorders in women. This lack of inclusion restricts the evidence base for treatment in women, perpetuating challenges in providing gender-specific clinical care.

The aim of this review is to provide a comprehensive summary of the distinctive characteristics of hereditary bleeding disorders in women, with a particular focus on HMB and other gynecological clinical challenges. It is beyond the scope of this review to describe detailed hemostatic treatments for all inherited bleeding disorders. Readers are therefore encouraged to consult recent guidelines and experts' recommendations on this topic.[12–16]

The terms "girls" and "women" are used throughout this article because most individuals with female genital organs identify as female; however, we refer to all individuals with ovaries and a uterus, regardless of their gender identity.

Heavy Menstrual Bleeding: Definition and Evaluation

HMB is defined as excessive menstrual blood loss that interferes with an individual's physical, social, or emotional quality of life.[17] Previous studies have considered a blood loss of >80 mL/cycle as excessive.[18] The European Hemophilia Association has suggested the 7:2:1 rule to help identify HMB. If a menstrual period lasts longer than 7 days, menstrual products (such as pads or tampons) have to be changed <2 hourly, or clots larger than the size of a 1-euro coin are passed, HMB should be considered (https://www.ehc.eu/

ehc-womens-committee-marks-2024-international-womens-day/ accessed 10.09.2024). In addition, nightly flooding, iron deficiency with or without anemia, and missing social activities due to menstrual blood loss may also indicate the presence of HMB.[19]

The Pictorial Blood-loss Assessment Chart (PBAC) is a semi-objective method to help quantify an individual's blood loss per menstrual cycle.[20] The tool has been applied and validated for clinical use and across various age groups.[21,22] A score of >100 indicates a blood loss of >80 mL. Of note, this score should be used prospectively for accurate results. If used retrospectively, it is prone to recall bias, as the patient is asked to describe how many menstrual products were used per day in previous cycles. Pictorial assessment of bleeding loss assessment is the preferred tool for establishing HMB as highlighted in a recent systematic review.[23]

Heavy Menstrual Bleeding: General Clinical Overview

HMB affects up to 90% of women and girls with a previously diagnosed bleeding disorder.[24,25] It is important to prepare and educate premenarchal girls and their families with anticipatory guidance about HMB. Symptoms and management should be explained so that the girl and her family can recognize HMB, and present to their health care center for HMB management promptly, ideally before an iron deficiency or anemia develops.

Girls and women without a prior diagnosis of a bleeding disorder may also present with HMB. It has been reported that 30 to 40% of women experience HMB during their reproductive years.[19,26] Of these, it is estimated that 20 to 30% have an underlying bleeding disorder.[27,28] Other causes of HMB include ovulatory dysfunction, endometrial disorders, iatrogenic causes, and structural conditions (adenomyosis, polyps, leiomyomas, hyperplasia, or malignancies).[29] Structural causes are more common in adult women than in adolescents.

Diagnosis of bleeding disorders in women and girls is often delayed because symptoms are treated without the necessary diagnostic tests.[30] In the "Rare Bleeding Disorders in the Netherlands" (RBiN) study, despite the presence of HMB since menarche, the diagnosis of a hereditary bleeding disorder was made at the age of 28 years on average.[31] Thus, it appears evident that the correlation between HMB and hereditary bleeding disorders remains insufficiently acknowledged. In a retrospective, population-based American study, among 23,888 adolescent girls with HMB, less than 20% had a von Willebrand factor (VWF) test at follow-up.[32] Similarly, a study based on an online questionnaire distributed to 183 gynecologists in 22 countries showed that only 12% of the experts surveyed initially considered a hereditary bleeding disorder as the cause of HMB.[33] The majority of respondents (62%) referred the patient to a hematology consultation only after 1 to 5 years of ineffective hormonal treatment. Cultural and societal factors may also contribute to the underreporting of symptoms, further complicating timely diagnosis and appropriate management.[34]

HMB has a profound impact on the psychological well-being of women. It can result in chronic pain, anxiety, and a decreased quality of life.[35] An early recognition of symptoms and a comprehensive clinical evaluation are crucial for minimizing the risk of complications, which include iron-deficiency anemia, the necessity for transfusions, hospital admissions, increased rates of missed days at school or work, fatigue, and psychological distress.[36–38]

Heavy Menstrual Bleeding: Investigations of an Underlying Bleeding Disorder

Girls and women presenting with HMB should be further evaluated with a bleeding history and diagnostic testing. If a bleeding disorder is suspected, the patient should be referred to a hematologist, ideally to a joint gynecology and hematologic clinic. Evaluating a bleeding history cannot be accurately achieved by using the overly simplistic "Do you have a bleeding disorder." To gain a comprehensive understanding of the patient's bleeding symptoms, it is essential to conduct a thorough assessment through a detailed bleeding history. The ISTH-BAT (International Society on Thrombosis and Hemostasis Bleeding Assessment Tool) is an established tool that has been standardized and validated for use in VWD, hemophilia carriers, fibrinogen disorders, and IPFDs.[39–42] The ISTH-BAT is completed by a health care provider while interviewing the patient. The self-BAT can be completed by the patients themselves.[43] A score of ≥6 in women or ≥3 in children is considered abnormal. Nevertheless, a recent publication has shown variability in these normal thresholds for women depending on their age[44] and a score adjusted to the age has been proposed (►Fig. 2).[45] A cohort study indicates that an ISTH-BAT score of ≥5 may be a useful indicator for identifying teenage girls with HMB and an underlying bleeding disorder, as demonstrated by ROC curves.[46] A family history of bleeding disorders, symptoms, and familial HMB can help identify bleeding disorders according to their inheritance. It may be helpful to quantify menstrual bleeding in family members by means of the PBAC, as the concept of "normal menstrual bleeding" is very variable, and often a construct of social, cultural, or stigma perceptions.[30]

The clinical examination is important as some findings may be indicative of an underlying diagnosis. The presence of telangiectasias around the lips or on the fingertips is commonly reported in HHT, which is more specifically characterized by the Curacao score.[47] Joint hypermobility tested by the Beighton score associated with skin hyperextension is a particular manifestation of Ehlers-Danlos syndrome (EDS).[48]

If there is clinical suspicion of a bleeding disorder based on the patient's presentation, PBAC, ISTH-BAT score, family history, and clinical examination, then specialized laboratory testing should be performed. It is important to note that the standard coagulation screening tests can be normal in affected individuals, and therefore are not sufficient to exclude the possibility of a bleeding disorder.[19] Laboratory tests should be performed in an outpatient setting and in a stepwise approach (►Fig. 2).[49] The initial laboratory tests

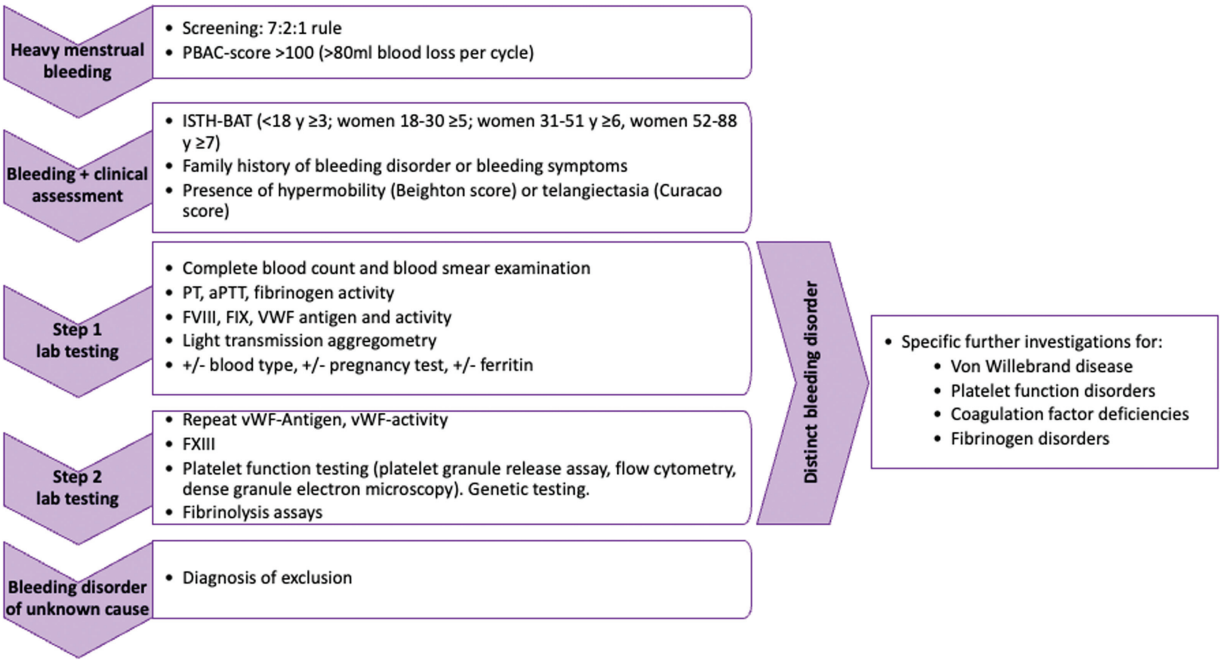

Fig. 2 Clinical and laboratory evaluation of a bleeding disorder in girls and women with heavy menstrual bleeding.

should include a complete blood count with an examination of the peripheral blood smear, prothrombin time, activated partial thromboplastin time, fibrinogen activity, activities of coagulation factors VIII and IX, measurement of VWF activity and antigen, and light transmission aggregometry. If no bleeding disorder is identified from the first laboratory tests, further testing may include repeating the VWD screening, measuring FXIII, fibrinolysis assays, and additional platelet investigations (e.g., assessment of platelet granule release, expression of major platelet surface glycoproteins by flow cytometry, genetic testing, electron microscopy). If all diagnostic tests are negative, the diagnosis of a bleeding disorder of unknown cause (BDUC) should be considered.[45]

Heavy Menstrual Bleeding and Hereditary Bleeding Disorders

Hemophilia is an x-linked bleeding disorder, but it is unknown precisely how many women are carriers of hemophilia mutations. It is estimated that there are three to five hemophilia carriers for every affected male.[50] One in three hemophilia carriers has low (<50%) factor VIII or IX levels which are presumed to be associated with causative mutation, chromosome x lyonization, VWF levels, and the ABO blood type.[7] Recently, a new nomenclature has been proposed considering women with factor levels below 40% as women with hemophilia. Women with bleeding symptoms and factor levels >40% should be referred to as symptomatic hemophilia carriers, and the rest are referred to as asymptomatic hemophilia carriers.[51] Up to two-thirds of girls and women who are carriers of hemophilia mutations present with various bleeding symptoms.[26] A prospective multinational study reported that HMB was the most common bleeding symptom in hemophilia carriers.[39] In a survey study conducted in the Netherlands including 274 women with hemophilia or carriers, the risk of requiring iron supplementation and hysterectomy was higher than that in healthy women.[52]

VWD affects ~1 in 1,000 individuals presenting to primary care with bleeding symptoms.[53] In a systematic review of 11 studies comprising 998 women with HMB, the prevalence of VWD was reported to be 13% (95% CI: 11–15.6).[54] In a prospective multicenter study of 200 adolescents with HMB, low VWF levels were the most common bleeding disorder identified. In this cohort, 16% of participants had low VWF levels, and 11% had a VWD.[55] HMB is the main contributory bleeding symptom, with up to 78 to 92% of women with VWD suffering from it.[54,56]

In women with severe PFD and RBDs, the prevalence of HMB is estimated to be between 50 and 100%, and 36 and 70%, respectively, depending on the severity of the disease, the definition of HMB, and the methods of assessing menstrual blood loss, ethnicity, and ABO blood group.[53,57–62] Characteristically platelet function disorders are associated with mucocutaneous bleeding, which includes HMB. In two prospective multicenter studies investigating HMB in adolescents, platelet function disorders were the second most common bleeding disorder (4.5 and 7%, respectively), after VWD.[55] The available data on specific coagulation factor deficiencies are limited. In a study comprising 234 women with factor VII deficiency, mucocutaneous bleeding was identified as a significant predictor of subsequent gynecological bleeding (HR = 12.8, 95% CI: 1.68–97.6).[63] The International Society on Thrombosis and Hemostasis (ISTH) Bleeding Assessment Tool (BAT) showed a positive correlation between the PBAC score and the factor VII deficiency.[64] A systematic review identified 121 women with factor XIII, for whom HMB was the second most common bleeding

symptom (26% of cases).[65] Similarly, women with factor XI deficiency also have a significantly increased risk of HMB, with a prevalence estimated between 7 and 67% depending on the series of patients.[62] In women with fibrinogen disorders, HMB is a very frequent issue. More specifically, in a large cohort of women with afibrinogenemia ($n = 101$) and dysfibrinogenemia ($n = 68$), 75 and 30%, respectively, reported experiencing HMB.[60,66] In the Dutch cohort study "Rare Bleeding Disorders in the Netherlands" (RBin), HMB was reported in 80% (89/111) of patients, especially in women with fibrinolytic diseases.[31]

In women with HHT, mucocutaneous bleeding is particularly manifest. Nevertheless, in a recent case–control study, the risk of HMB was decreased in women with HHT compared with age-matched women with VWD (OR: 0.32; 95% CI: 0.18–0.57; $p \leq 0.0001$).[67] A bleeding phenotype is a common clinical feature of EDS. In a recent case–control study of 52 patients, HMB was the most common bleeding symptom (84% of women), including 7 (14%) episodes that were life-threatening or requiring surgery.[68]

Heavy Menstrual Bleeding Complications: Iron Deficiency with/without Anemia

It has been reported that iron deficiency affects 9 to 12% of women of reproductive age worldwide (https://www.who.int/publications/i/item/9789241564960, last accessed October 31, 2024). HMB is a major cause of iron deficiency, and iron deficiency is the most common cause of anemia,[26] especially in women with a bleeding tendency.[69] In a recent survey of 120 women with low VWF, HMB was reported in 86% with 46% developing iron deficiency and 12.5% requiring hysterectomy or endometrial ablation.[70] In adolescents with HMB seen in a specialized hematology clinic setting, iron deficiency without and with anemia were reported in 24 and 37%, respectively.[28] Iron deficiency can be an indicator of HMB if the symptom of HMB has not yet been objectified or identified. Often, girls and women affected by iron deficiency will receive iron supplements orally or intravenously. This is a symptomatic treatment only, and girls and women with HMB are continuously at risk of recurrent iron deficiency. Therefore, it is prudent to consider HMB and a bleeding disorder as a differential diagnosis in every girl or woman presenting with iron deficiency with or without anemia.

Hormonal Treatment of Heavy Menstrual Bleeding

Hormonal therapy is an effective method for controlling HMB.[12] Hormonal medications stabilize and reduce the endometrium thickness, which in turn leads to a reduction in menstrual blood flow and, in some cases, to amenorrhea. In the absence of uterine pathology or pregnancy wish, these medications are considered the first line of therapy for individuals with HMB. In the absence of data regarding the impact of hormonal medications on menstrual management in individuals with bleeding disorders, treatment approaches are based on evidence from the general population.[71] Hormonal medications include estroprogestative and progestin-only methods (►Table 1). When choosing among the various available options, several aspects should be considered, including endometrium thickness, potential individual contraindications, the necessity for contraception, and patient preferences.

Estroprogestative methods include the combined oral contraceptive pill, the contraceptive patch, and the vaginal ring. These methods have been demonstrated to result in a 70% reduction in menstrual blood flow.[72] In addition, they suppress ovulation, which may consequently prevent complications associated with ovulation bleeding. These methods may be used cyclically (monthly withdrawing bleeding) or in a continuous manner with the objective of reducing the frequency of menstrual bleeding episodes. Given the absence of a physiological rationale and the absence of a health benefit associated with hormone-free interval and withdrawal bleeding, extended or continuous use of estroprogestative methods may be recommended for individuals with HMB. Progestin-only methods are associated with inconsistent ovulation suppression and irregular bleeding menstrual patterns. The 52-mg levonorgestrel intrauterine device (LNG IUD) has been demonstrated to result in a 94% reduction in menstrual blood flow and a 60% amenorrhea rate at 1 year.[73] There are contrasting data about the use of LNG IUD in women with bleeding disorders. Concerns about potential higher rates of LNG IUD expulsion or malposition and early discontinuation in women with bleeding disorders have been raised.[74,75] However, other studies have demonstrated the effectiveness of LNG IUDs in this population, with outcomes comparable to those observed in the general population.[76,77] It is essential that individuals be informed of the potential for unscheduled bleeding, particularly during the initial 3-month period following insertion. The progestin-only pill (also known as the minipill) and the subdermal contraceptive implant are associated with a high risk of breakthrough bleeding and therefore are not considered as first-line therapy for HMB.

Hemostatic Management Options for Heavy Menstrual Bleeding

Hemostatic therapy can be used on its own, or in conjunction with hormonal treatment, as necessary. Hemostatic management options include the use of antifibrinolytics, desmopressin, and factor or non-factor replacement therapies.[12,78,79] Given their antiplatelet effects, nonsteroidal anti-inflammatory drugs are not recommended in women with bleeding disorders. Tranexamic acid is the most studied antifibrinolytic agent used for HMB and has shown efficacy in reducing menstrual blood loss.[25,80] Desmopressin can be used in patients with VWD and hemophilia A, provided that a positive response has been previously demonstrated. It can also be used in patients with mild platelet disorders or BDUC.[13] In girls and women with factor deficiencies where HMB is not controlled with hormonal treatment or tranexamic acid, replacement of the specific factors has been shown to be effective for the

Table 1 Overview of hormonal therapies for girls and women with heavy menstrual bleeding

Hormonal medications	Formulation	Dosing for acute management of HMB	Dosing for maintenance	Side effects, special considerations
Estroprogestative methods				
Combined oral contraceptive pill	Various formulations	1 tablet QID (EE 30–50 µg/ LNG 150 mg)	Oral daily, cyclic (21/7), or continuous use	Nausea, breast tenderness, headaches, fluid retention, metabolic changes, risk of breakthrough bleeding, risk of venous and arterial thrombosis
Combined hormonal patch	EE 60 (or 75) µg/norelgestromin 6 mg	NA	Weekly, cyclic (21/7), or continuous use	
Combined hormonal vaginal ring	EE 270 µg/etonogestrel 11.7 mg	NA	Monthly, cyclic (21/7), or continuous use (change every 3–4 wk)	
Progestin-only methods				
Hormonal IUD	52-mg levonorgestrel IUD	NA	Duration of 8 y	Risk of breakthrough bleeding especially during the first few months after insertion
Oral progestin	Norethisterone acetate	5–10 mg QID	5–10 mg oral daily or BD	Headaches, acne; not contraceptive
	Medroxyprogesterone acetate	10–20 mg BD-QID	10–20 mg oral daily or BD	
Injectable progestin	Depot medroxyproges-terone acetate	NA	150 mg intramuscular or 104 mg subcutaneous injection every 12 wk	Risk of intramuscular hematoma (favor subcutaneous injection in people with bleeding disorder), headaches, fluid retention, weight gain, low bone mineral density, and risk of breakthrough bleeding
Progestin-only pill	Various formulations	NA	Oral daily, continuous use	Not considered as first-line therapy for HMB because of the high risk of breakthrough bleeding
Implant	68-mg etonogestrel	NA	Duration 3 y	Not considered as first-line therapy for HMB because of the high risk of breakthrough bleeding
GnRH agonists				
	Various formulations (leuprolide, goserelin, triptorelin, histrelin)	NA	Variable dosing (monthly, 3–monthly, 6–monthly, or annually)	Low bone mineral density, “menopause-like” symptoms; not contraceptive

Abbreviations: BD, twice a day; EE, ethinyl estradiol; GnRH, gonadotropin-releasing hormone; HMB, heavy menstrual bleeding; IUD, intrauterine device; LNG, levonorgestrel; NA, not applicable; QID, four times a day.
Note: The availability of medications differs across countries.

management of HMB. Other options for factor replacement include fresh plasma, prothrombin complex concentration, or cryoprecipitate.[3] A platelet-sparing hemostatic management approach is typically preferred due to the risk of alloimmunization, particularly in severe platelet function disorders. However, an optimal platelet transfusion strategy remains to be established.[81]

Other Gynecological Bleeding

In addition to HMB, women are susceptible to other specific hemorrhagic complications.[82] While ovulation is typically not accompanied by any significant bleeding, in women with bleeding disorders it can result in bleeding into the follicular sac, the peritoneum, the broad ligament, and the retroperitoneum.[83] In a series of 210 patients with RBDs, 68 (32.4%) were confirmed to have hemorrhagic ovarian cysts by clinical and ultrasound examination.[84] In women with the most severe RBDs, hemorrhagic ovarian cysts may be complicated by significant internal bleeding. A systematic literature review of 104 women with factor XIII deficiency revealed that 10% of them experienced intraperitoneal bleeding after ovulation.[65] Similarly, a systematic literature review on factor X deficiency reported that hemoperitoneum occurred in 8 out of 322 women.[85] In women with afibrinogenemia, recurrent hemoperitoneum is a frequent complication.[86] Furthermore, women with bleeding disorders may be more prone to heavy bleeding associated with anovulation, which typically manifests after menarche and during the perimenopausal period.

A case–control study conducted by the United States Centers for Disease Control and Prevention comprised 102 women with VWD and found that endometriosis, fibroids, endometrial hyperplasia, and endometrial polyps were significantly more prevalent in the case group than in the control group.[87] It is unknown whether women with bleeding disorders are more prone to developing endometrial hyperplasia, fibroids, or polyps, but it is probable that they will experience more pronounced symptoms than women without a bleeding disorder. Furthermore, these conditions may also reveal a previously subclinical bleeding tendency and, in a woman with a bleeding disorder, may result in significant bleeding.[8] The incidence of hysterectomy is higher among women with bleeding disorders than in those without, and the procedure is more likely to be performed at an earlier age.[88] In a large database study that included 545 women with VWD who underwent hysterectomy, those with VWD were significantly more likely to experience periprocedural bleeding and require transfusion than women without VWD.[89] Conversely, a national observational study revealed that the prevalence of VWD screening in the 12 months preceding hysterectomy was exceedingly low, confirming the necessity to enhance awareness that a bleeding disorder may be a contributing factor to HMB, even in the presence of gynecological disease.[90] Similar findings have been reported in women with factor XI and FXIII deficiencies.[62,65]

Pregnancy and Delivery

The rate of miscarriages is not typically increased in women with hereditary bleeding disorders, except in women with severe factor XIII deficiency or with fibrinogen disorders. This highlights the crucial role of factor XIII and fibrinogen during pregnancy. In a systematic review of 192 pregnancies in women with factor XIII deficiency, two-thirds resulted in miscarriage, including 25% of recurrent miscarriages (defined as three or more nonconsecutive pregnancy losses).[65] In a series of 425 pregnancies in women with hypofibrinogenemia or dysfibrinogenemia, 55 (12.9%) pregnancies resulted in an early miscarriage without statistically meaningful differences between hypo- and dysfibrinogenemia.[91] However, higher rates of miscarriages have been reported in women with thrombotic-related dysfibrinogenemia[92] and in a recent retrospective cohort of 123 women.[93] Overall, miscarriage rates are significantly improved by introducing the factor deficient in early pregnancy.

Pregnant women with bleeding disorders require specialized peripartum care to prevent postpartum hemorrhage (PPH), which is more prevalent in these patients than in healthy women. In a retrospective study conducted on 185 deliveries in 154 women with VWD or hemophilia carriers, PPH was observed in 62 (34%) deliveries.[94] A recent systematic literature review on hemophilia carriers, which described 502 deliveries, identified an incidence of PPH of 63%.[95] Similarly, women with RBDs are at an increased risk of PPH. In the RBiN study, a total of 244 pregnancies, including 193 live births, were reported by 85 women. A significant proportion of these women experienced PPH, with rates ranging from 30% in factor V deficiency to 100% in hyperfibrinolysis. Overall, PPH was reported in 44% of deliveries performed with and 53% of deliveries performed without administration of peripartum hemostatic prophylaxis.[31] A multicenter retrospective cohort study demonstrated that women with fibrinogen disorders are at significant risk of PPH, particularly those with dysfibrinogenemia and a bleeding phenotype observed prior to the delivery.[66] A multidisciplinary approach involving anesthesiologists, hematologists, neonatologists, and obstetricians, preferably affiliated with a bleeding center, may reduce obstetric morbidity in women with bleeding disorders.

Conclusion

Hereditary bleeding disorders present distinctive challenges for girls and women, largely due to the sex-specific nature of bleeding symptoms that may have a profound impact on the quality of life. Effective management requires increased awareness among healthcare professionals, early diagnosis, and individualized treatment approaches that consider both hormonal and hemostatic options. Addressing these needs has the potential to improve health outcomes for girls and women with bleeding disorders. Continued advocacy, research, and education are essential to ensure equitable

care and reduce gender bias in the management of bleeding disorders.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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