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Women and inherited bleeding disorders – A review with a focus on key challenges for 2019

R. Winikoff[a,*], M.F. Scully[c], K.S. Robinson[b]

[a] Division of Hematology-Oncology, Sainte-Justine University Hospital Center, Montréal, QC, Canada
[b] Division of Hematology, Dalhousie University, Queen Elizabeth II Health Sciences Centre, Department of Medicine, Halifax, NS, Canada
[c] Department of Medicine, Memorial University of Newfoundland Medical School, NL, Canada

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ABSTRACT

The area of women and inherited bleeding disorders has undergone quick expansion in recent years. More patients are being identified and expertise to diagnose and manage these patients is now essential for practising physicians. Programs to help educate and empower patients and caregivers are now in place. Common inherited bleeding disorders affecting women include von Willebrand disease (VWD), inherited platelet disorders, and rare inherited bleeding disorders such as factor VII (FVII) deficiency and factor XI (FXI) deficiency. Specific clinical tools have been developed to help clinicians and patients screen for the presence of these bleeding disorders in both adult and pediatric populations. Affected women can experience heavy menstrual bleeding and resulting iron deficiency anemia, postpartum hemorrhage, and hemorrhagic ovarian cysts which need to be properly managed. Excessive bleeding can adversely affect quality of life in these women. Front line therapy for bleeding in mild cases focuses on the use of non-specific hemostatic agents such as DDAVP ®, tranexamic acid and hormonal agents but specific factor replacement and/or blood products may be required in more severe cases, in severe bleeding or as second line treatment when bleeding is not responsive to first line agents. Iron status should be optimised in these women especially in pregnancy and use of an electronic app can now help clinicians achieve this. These patients should ideally be managed by a multidisciplinary team whenever possible even remotely. Although clinical research has closed some knowledge gaps regarding the diagnosis and management of these women, there remains significant variation in practise and lack of evidence-based guidelines still exists in many spheres of clinical care in which caregivers must rely on expert opinion. Ongoing efforts in education and research will continue to improve care for these women and restore quality of life for them.

1. Introduction

After a landmark study reporting on the challenges faced by women with bleeding disorders was published in 1998 [1], this important clinical challenge began to receive more attention in the wider medical community. Obstetricians and gynecologists were long focused on both gynecologic and obstetric causes of bleeding as were all those involved in blood banking in hospitals with maternity units. Specifically, pediatric and adult hematologists became more aware of the challenges of women living with inherited bleeding disorders and interest grew in the hereditary bleeding disorders community. However, it has been much more difficult to increase awareness and interest at the level of primary care, emergency care and generalist physician level.

Addressing the gaps in care for women with inherited bleeding disorders has been an increasing focus of interest over the past decade. In this time period, we have seen a changing trend worldwide with an increase in the number of clinics offering specialized care for women with bleeding disorders, as well as research, increased publications, focus at scientific conventions and national advocacy efforts in this area. The number of newly diagnosed patients with inherited bleeding disorders is increasing [2] as is the number of women registered in multidisciplinary hemophilia clinics across North America [3,4] making it important for physicians to feel confident treating excessive bleeding in these women.

National guidelines have been published although evidence-based management is still lacking in many spheres of clinical care. This review will highlight some of the changing trends in women with inherited bleeding disorders. It will review the common inherited bleeding disorders which affect women as well as common bleeding symptoms and their management including menorrhagia, postpartum

* Corresponding author at. Division of Hematology-Oncology, Sainte-Justine University Hospital Center, Montréal, QC, Canada.
E-mail addresses: dr.mfscully@hemostasis.c (M.F. Scully), sue.robinson@nshealth.ca (K.S. Robinson).

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hemorrhage and will also briefly outline the management of hemorrhagic ovarian cysts. Particular clinical challenges and areas of interest for clinical studies will be highlighted as will some new programs and clinical tools that are now available to patients and their caregivers.

2. Background: perspective

The World Federation of Hemophilia global survey data demonstrates a steady increase in the number of individuals diagnosed with inherited bleeding disorders i.e. von Willebrand disease (VWD), hemophilia, platelet dysfunction and rare bleeding disorders [5]. This trend can be partly explained by improved screening efforts by physicians and by improved access to care in some countries, but may also be related to increased transmission of these disorders due to increased longevity among affected individuals secondary to major improvements in the safety of the blood supply.

Women are disproportionately represented in most inherited bleeding disorder registries largely due to excessive genital tract bleeding and comprise up to 2/3 of patients in most registries [2].

Heavy menstrual bleeding since menarche, hemorrhagic ovarian cysts, and antepartum and postpartum bleeding are specific challenges faced by women and girls with inherited bleeding disorders [6]. Miscarriages may be more frequent among some women with inherited bleeding disorders [3,6,7]. Specialized care with appropriate hemostatic management is required to manage these women in order to avoid unnecessary transfusions, hospitalizations and to minimize postoperative or peripartum/postpartum bleeding. This expertise is also essential to ensure the safe delivery of a baby with moderate or severe hemophilia or any severe bleeding disorder.

Finding the best care paradigm for women with bleeding disorders in our modern highly complex health-care systems is quite a conundrum. Traditionally, women's health has been the major focus of obstetricians and gynecologists and also a major focus of family medicine. Since the traditional hemophilia's are X-linked and are the commonest severe hereditary bleeding disorders, Hemophilia Treatment Centers were initially created to support boys and men. Their initial needs outside a hematological lens were for extra help from physiotherapy and orthopedics because muscle and joint bleeds are severe and challenging problems for hemophilia patients. For women with inherited bleeding disorders, although rarely they can suffer from the same significant musculoskeletal problems as men, more frequently the needed links are with family medicine, obstetrics and gynecology and public health. Efforts to offer optimal care for women are now becoming a priority in many countries worldwide.

A multidisciplinary team approach in large tertiary care centers is considered the optimal care paradigm for women with inherited bleeding disorders [8,9]. This administratively heavy arrangement may be difficult to organize in smaller peripheral centers and in remote rural regions with limited resources. The absence of a local interdisciplinary team may be challenging for primary care physicians, nurse practitioners and nurses caring for these women. At all times, good communication between the hematologist or internist/pediatrician and the obstetrician-gynecologist is essential to manage affected patients. Gynecological procedures, surgery and deliveries for women and/or their babies at high risk of bleeding are ideally managed in a tertiary care Hemophilia Treatment Center with a full multidisciplinary team and fully operational blood bank [10–12]. Given the geography of Canada, this is not always an ideal option, as it means that an expectant mother will be separated from her community at a very important time in her life. At the very least, input from a multidisciplinary team [13] as well as ensuring access to appropriate, individualized therapy is essential for a safe treatment plan. Going forward, we can explore using video, smart-phones and other new forms of technology to link into needed expertise. Telehealth is already being used to help manage persons with bleeding disorders remotely [14].

3. Clinical challenges and screening

Abnormal uterine bleeding may be the very first sign of an underlying bleeding disorder and should prompt the physician to consider hemostatic testing. At presentation, abnormal bleeding must still be managed even if a bleeding disorder has not yet been identified. Establishing an accurate diagnosis is essential to optimize treatment and ideally to reduce the risk for and minimize future bleeding events. Clinically, refractoriness to first line hormonal treatment [15], heavy menstrual bleeding since menarche [16], hemorrhagic ovarian cysts [7] and delayed postpartum bleeding [16] are all symptoms that may suggest an underlying bleeding disorder. Additional bleeding symptoms accompanying heavy menstrual bleeding or a family history of bleeding is also suggestive of a possible underlying bleeding disorder [17].

Access to care for patients with gynecological and obstetrical bleeding may be hampered by factors such as lack of a primary care physician and long wait-lists. A lack of insurance coverage and a rural setting may also hamper accessibility to medical care. Limited resources and economic constraints of different countries may also play an important role [18].

Although the proportion of physicians screening for underlying bleeding disorders in symptomatic women has increased over the last decade [19,20] still only 8% of all patients with heavy menstrual bleeding (16% of those with severe symptoms) were screened in a recent study [21]. Screening for VWD prior to hysterectomy was very low in a cohort of women with health care insurance and heavy menstrual bleeding; rural inhabitance and longer distance from the nearest Hemophilia Treatment Center within a metropolitan were associated with lower chance of being screened [22].

Programs such as Code Rouge in Canada, launched by the Canadian Hemophilia Society, and the Foundation for Women and Girls with Blood Disorders in the USA have been developed specifically to increase awareness and educate patients and their health care providers on issues related to women and girls with inherited bleeding disorders. These programs also aim to ensure that women have access to appropriate care. Patient awareness and self-education may prompt more symptomatic women to seek medical attention from their local healthcare providers or local/national foundations. Also, physician education will hopefully continue to improve the prevalence of bleeding disorder screening among symptomatic women.

Standardized Bleeding Assessment Tools (BAT), with applied age and gender cutoff scores can be used to screen women and girls for an underlying bleeding disorder to decide if further testing is required although the presence of heavy menstrual bleeding alone can also uncover a high percentage of bleeding disorders. (23)BATs have evolved from their original format developed primarily as research tools [24,25] to screen individuals for VWD to more practical clinical ones [26]. Disease specific BATs, both physician and self-administered, have been developed for VWD [26,27] carriers of hemophilia [28,29] and for some pediatric populations as well [30,31]. A Let's Talk Period global website (https://**letstalkperiod**.ca) has been created with online access to a self–BAT for women with bleeding symptoms to screen themselves for inherited bleeding disorders [32].

Seventeen per cent (17%) of women presenting with heavy menstrual bleeding will have an underlying inherited bleeding disorder [23]. VWD is the most commonly found inherited bleeding disorder among women and girls presenting with heavy menstrual bleeding with numbers ranging from 12% [23] to as high as 36% in some tertiary care hemophilia referral centers [33,34]; these higher numbers may in part be explained by referral bias. Rates are also increased among women and girls hospitalized for heavy menstrual bleeding, those with severe symptoms, those requiring transfusion and those whose symptoms are present since the menarche [35]. Recent data suggests that the presence of an underlying inherited bleeding disorder may be as common among women with an ovulatory bleeding as in ovulatory bleeding. (personal communication) In addition, testing for VWD in adolescents with heavy

menstrual bleeding has been shown to be cost effective [36].

Heavy menstrual bleeding can significantly impair quality of life in affected patients and can lead to significant work and school absenteeism [1]. Affected women also suffer a negative psychological impact [37–39]. In addition, there are increased direct and indirect hospitalization costs related to anemia from gynecological and obstetrical bleeding in women with inherited bleeding disorders [40,41]. Excessive blood loss in these women often leads to Iron deficiency anemia which can cause significant morbidity [42,43] among affected women and therefore must be adequately treated. Further, acquired platelet dysfunction from iron deficiency may exacerbate bleeding in these women [34,44].

4. Hereditary bleeding disorders affecting women- prevalence, transmission and diagnosis

4.1. Von Willebrand Disease (VWD)

Von Willebrand Disease is the single most common inherited bleeding disorder with a prevalence of 1/100 and symptomatic prevalence of 1/1000 [45]. VWD is a family of disorders related to mutations in the VW factor (VWF) gene coded on chromosome 12. The complex interaction between circulating VWF and platelets is key to primary hemostasis. VWF multimers also bind the procoagulant zymogen Factor VIII (FVIII) and is highly protective of FVIII from proteolytic cleavage. The most common subtype of variable severity is type 1 and type 3 is both the most severe and the most uncommon form of VWD. Each is characterized by decreased levels of circulating VWF inherited in an autosomal dominant and autosomal recessive manner, respectively. Type 2 makes up anywhere from 20 to 30% of all VWD types. In type 2 VWD subjects have a normal quantity of multimeric protein but functional defects, which affect the multimers ability to function normally in their role in primary hemostasis and/or as a carrier of FVIII. The percentage of type 2 may be as high as 60% if stringent criteria are applied to type 1 (VWF $<$ 30 U/l) [46].

Laboratory analyses are fraught with a slew of preanalytical variables that affect the results including delays in specimen transportation and processing. Hormones, especially estrogen, pregnancy, physical and mental stress, aging and certain medical conditions can all significantly increase measured levels of VWF [10] thus making diagnosis of mild cases particularly challenging. In addition, tests of von Willebrand function are subject to large laboratory coefficients of variation and a large intra-patient variability posing difficulty for VWD diagnosis distinguishing between type 1 VWD and type 2 VWD. Treatment response to DDAVP® (desmopressin acetate) and factor replacement may differ between the two subtypes therefore making accurate diagnosis important. Genetic testing is not yet widely available for clinical use although some clinical platforms do exist. The von Willebrand gene has 52 exons making mutation analysis laborious, especially in type 1, where causative mutations may span across the entire gene including the promotor region. In contrast mutations for type 2 tend to be clustered around certain regions of the gene making targeted sequencing possible. Given these challenges to diagnosis, referral to specialized centers for testing is recommended.

4.2. Hemophilia A and B

Hemophilia is an X-linked disease and as such girls and women are carriers. The incidence of female carriers is not known. Up to 1/3 of FVIII mutations among female carriers occur sporadically and hence will not have a family history of hemophilia. By and large, the vast majority (˜ 80%) of female carriers have normal to low normal factor levels. Low factor levels in carriers is uncommon, occurring only in approximately 10–20% of women. Skewed inactivation of the X chromosome by excessive lyonization or the presence of rare genetic conditions (such as Turners syndrome) may lead to lower than expected FVIII or factor IX (FIX)levels in carriers. Carriers of hemophilia with decreased levels of coagulation FVIII or FIX may have symptomatic bleeding in the form of muscular and articular bleeding as in their male hemophilia counterparts. A study published in 2006 first reported that carriers with normal or near normal factor levels of 0.41-0.60 U/mL (40–60%) could still have a decreased quality of life related to heavy menstrual periods and iron deficiency in addition to increased bleeding from skin wounds, tooth extraction and surgery [47]. Recent studies suggest that carriers may have significant bleeding regardless of their factor levels [48–51]. Ongoing prospective studies are aiming to more clearly characterize the phenotypic bleeding patterns in carriers of hemophilia. (personal communication).

4.3. Inherited platelet disorders

There is significant uncertainty around the true frequency of platelet dysfunction among women with clinical bleeding. Estimates range from 2% to 44% among adolescents with menorrhagia in some studies [35,52,53]. Part of this variation may relate to differences in the sequence used for various laboratory testing; most centers use step wise testing starting with VWD testing and only proceed to platelet function testing if the von Willebrand profile is normal or equivocal while few do so upfront thus obscuring the true frequency. In addition, platelet function testing is precarious and is not standardized across laboratories partially explaining the variation in reported prevalence. Iron deficiency may cause acquired platelet dysfunction [44] and is not controlled for in most studies looking at diagnostic screening. A recent prospective study using rigorous platelet function testing methods revealed only a 4% prevalence of platelet function disorders [54] among women and girls presenting with menorrhagia. Bleeding in Bernard Soulier or Glanzmann Thrombasthenia is related to decreased or absent platelet surface receptors while other platelet function defects are related to aberrant secretion or altered signaling between platelets thus impairing their ability to either adhere to the vascular endothelium or to aggregate with other platelets, respectively. Receptor defects are inherited in an autosomal recessive manner whereas many other platelet defects may be inherited in an autosomal dominant pattern. A more detailed description of laboratory diagnosis of these disorders can be found in the article by Rand M et al. in part 1 of this series [55]

4.4. Rare inherited bleeding disorders

Factor VII (FVII) deficiency is the most frequent of the rare factor deficiencies with a reported prevalence of 1/500 000 [56]. It has an autosomal recessive inheritance. Mutations can give rise to deficiencies of a qualitative or quantitative nature. Severe cases have increased risk of intracranial or gastrointestinal bleeding especially in newborns. In adults, it often presents as mucocutaneous bleeding. Affected women have a propensity for uterine bleeding, in particular, heavy menstrual bleeding in addition to perioperative and postpartum bleeding. A more detailed discussion on FVII deficiency can be found in a paper by Robinson S in part one of this series [57].

Factor XI (FXI) deficiency is rare with a reported prevalence of 1/1 000 000 but more frequent among Jews of Ashkenazi descent and among consanguineous communities. It is most often transmitted in an autosomal recessive manner although rarely an autosomal dominant pattern of transmission is described [58]. Bleeding in affected individuals may be exaggerated postoperatively, especially in tissues with high fibrinolytic potential such as the uterus thus putting affected women at risk for heavy menstrual bleeding and postpartum hemorrhage particularly after an operative delivery. A detailed review on FXI deficiency can be found in a paper by Jain S and Acharya S in part 1 of this series [59].

5. Clinical bleeding manifestations

5.1. Heavy menstrual bleeding

Heavy menstrual bleeding is the most common bleeding manifestation reported in women with inherited bleeding disorders [60]. It was originally defined as menstrual bleeding during regular cycles that is excessive in quantity exceeding 80 cc/cycle. This definition is an impractical one since it relies on physical measurements of blood loss through pad and tampon collection and a laborious laboratory technique [61]. Subjective recognition of excessive menstrual bleeding is hampered by the fact that women and girls who bleed excessively may falsely conclude that their bleeding is normal when comparing to their mothers or sisters who may also have an underlying bleeding disorder and thus not report this to caregivers. Also, perceptions of quantity of blood loss may be variable from one individual to the next and may also be influenced by the type of sanitary protection used. Clinical correlates of heavy menstrual bleeding are imperfect but symptoms of duration greater than 7 days, changing protection more than hourly, staining night clothes, passage of clots and a low ferritin may be helpful on patient interview [62]. A semi-objective tool is a good compromise in assessing menstrual blood loss. Specifically, a score > 100 on the pictorial blood chart (PBAC) (Fig. 1) has a high specificity and sensitivity to diagnose menorrhagia and is easy to use [63]. It is available online for printing from the Canadian Hemophilia Society website (https://www.hemophilia.ca) and is even available in an electronic app (Me-Period Flow Assessment links iOS http://goo.gl/SuXlF5, Android: https://goo.gl/1KOpJU). It has the added value of being able to help substantiate a patient's complaints and may also be used to follow treatment response although it has not been specifically validated for this purpose. The Diva cup (and other similar products) is a reusable silicone device that can be inserted into the vagina to collect menstrual blood. It has the advantage of being able to directly measure a woman's monthly menstrual blood loss. More recent international definitions refer to heavy menstrual bleeding as a woman's perception of increased menstrual volume regardless of cycle regularity, frequency or duration and of sufficient quantity to impair a woman's quality of life thus obviating the need for measurement of blood loss in the clinical setting altogether [64,65].

Various treatment approaches for chronic heavy menstrual bleeding have been published. Of special note is that the treatment of heavy menstrual bleeding differs little between women with and without inherited bleeding disorders with very few exceptions. In women with established or suspected inherited bleeding disorders, NSAIDS are generally avoided due to their propensity to cause platelet dysfunction however they can be trialed for patients with mild bleeding disorders. Specific hemostatic therapies such as DDAVP® and specific factor concentrates can be added to the treatment options. Finally, surgery can lead to excessive bleeding [66–68] despite hemostatic coverage and thus surgical treatment options are approached with caution in patients with inherited bleeding disorders. A practical algorithm for the approach to heavy menstrual bleeding is shown in Fig. 2 [69]. This algorithm considers family planning decisions and the patient's desire to maintain fertility in the treatment choices. As in common practice, it defers invasive procedures and surgical approaches under appropriate hemostatic coverage to the last line but does not exclude these options when they are necessary [70].

Combined oral contraceptives, progesterone only pills and local

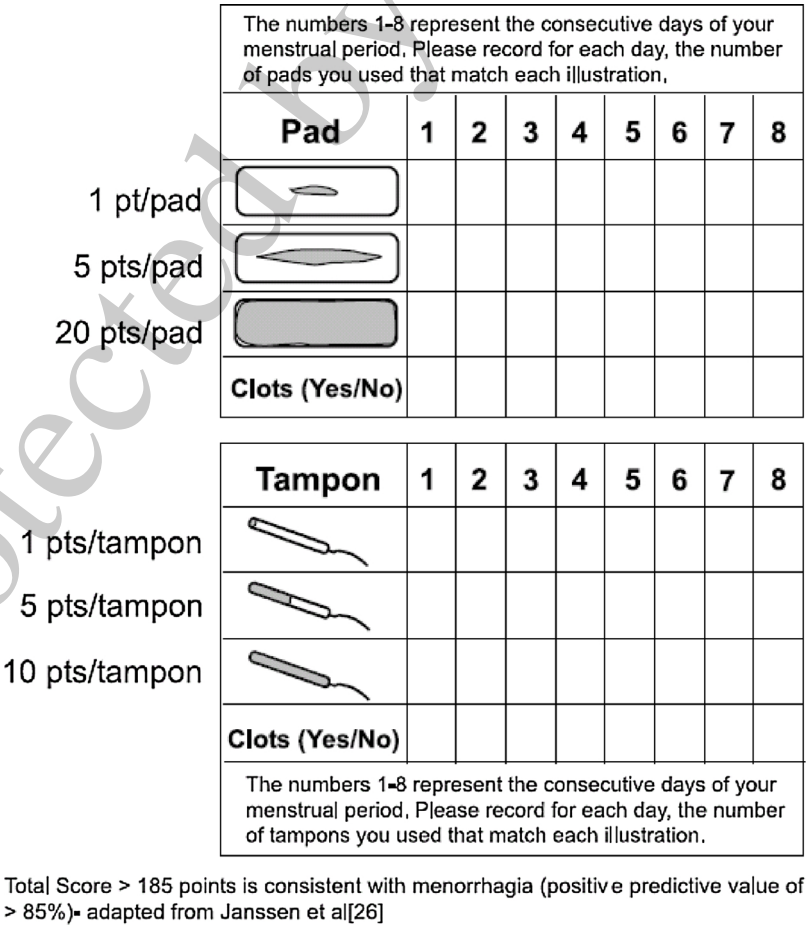

Fig. 1. Pictorial chart assessment of menstrual flow.
Source: Highams et al. Br J Obs Gyne, 1990.

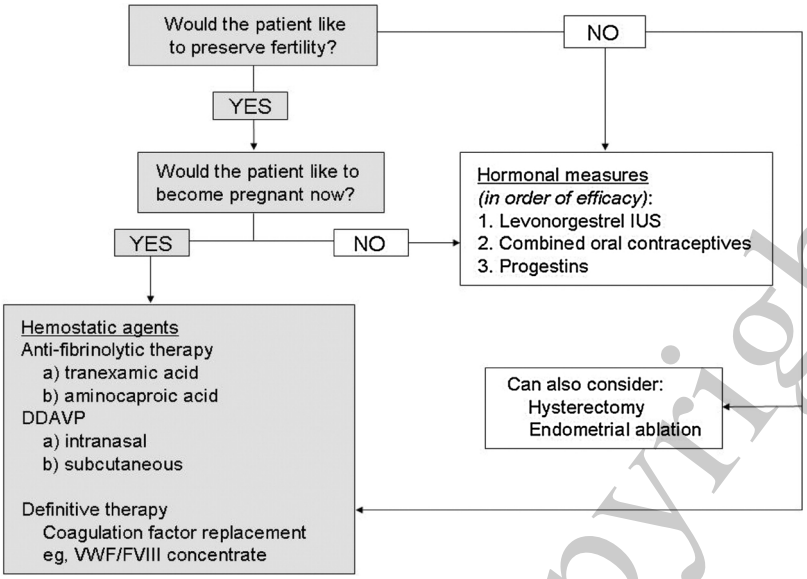

Fig. 2. Acute Heavy Menstrual Blood Loss Algorithm.
Source: *James AH et al.* Eur J Obstet Gynecol Reprod Biol. 2011 Oct;158(2):124-34.

hormonal treatments such as the levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena®) are all treatment options for women who do not wish to conceive in the short term especially if they require contraception. Continuous release of levonorgestrel from the system acts locally on the endometrium with its effect lasting up to 5 years. The levonorgestrel-releasing intrauterine system is the most effective non-surgical treatment of heavy menstrual blood loss and decreases menstrual blood loss by as much as 87% in women with and without inherited bleeding disorders [71,72]. Troublesome spotting may be a reason for discontinuation but usually resolves after the first 6 months. A high rate of expulsion and malposition [73] have been described in VWD patients possibly related to heavy blood back flow in women with heavy menstrual bleeding. Lower expulsion rates may be achieved by avoiding placement during menses, and administering appropriate hemostatic therapy prior to insertion, and during the first period after insertion (personal experience) but this remains to be determined in a prospective study. New smaller formats of hormonally impregnated progestogen intrauterine systems are now available and suitable for nulliparous women and adolescents (albeit with hormonal effect lasting 3 years rather than 5 with Mirena®) although these have not been studied specifically in the inherited bleeding disorder population.

There are no head to head trials showing any advantage of one oral combined contraceptive over the other [74]. Failure of low dose estrogen formulations, however, has been described in women with inherited bleeding disorders [45]. Combined contraceptives reduce menstrual blood flow by inducing shorter, regular shedding of a thinner endometrium. Additionally, combined contraceptives may also increase VWF and FVIII thus providing an additional benefit to women with bleeding disorders. The oral contraceptive pill is often the first line treatment for heavy menstrual bleeding in adolescents in most clinical practices, especially among those needing contraception. However, in some countries, cultural influences trend first line treatments in adolescents towards tranexamic acid [75]. Combined contraceptives can also be administered via dermal patch or vaginal ring.

Non-hormonal approaches should be used first in patients who wish to become pregnant in the short term. Tranexamic acid (Cyklokapron®) is effective to treat menorrhagia [76] and has been available in Canada for almost 5 decades and its slightly prolonged half-life counterpart Lysteda®, became available in the USA just a decade ago. A hallmark study conducted in the USA showed that tranexamic acid was just as good if not better than DDAVP® in treating heavy menstrual bleedings in women and girls with laboratory anomalies of hemostasis [77].

Tranexamic acid is a lysine analogue that binds plasmin preventing it from adhering to fibrin thus preventing clot breakdown. It is taken only on days of heavy menstrual blood flow and thus may improve compliance over oral contraceptives that must be taken daily. Although many doses and dosing schedules for tranexamic acid have been published; that of 1500 mg three times daily orally is most common. A dose finding study conducted in women with heavy menstrual bleeding with and without bleeding disorders showed that the median effective dose was 1000 mg twice daily [78], suggesting that lower doses may be equally as effective as the standard dose to treat heavy menstrual bleeding in these women. On average tranexamic acid decreases menstrual blood flow by 30% in responders; variability in response is reported although the reasons for this remain unclear. Side effects include symptoms such as dizziness and nausea but these respond to dose reductions and may be avoided if the dose is gradually increased. In general, tranexamic acid for the treatment of heavy menstrual bleeding is considered safe [79] although reports of thrombosis among patients with other known risks of thrombosis have been reported.

DDAVP® is an analogue of vasopressin and is available in IV, SC and intranasal formulations. Intranasal use has mostly been used to treat heavy menstrual bleeding in the home setting whereas IV and SC formulations are usually reserved for use in the hospital or clinic setting. DDAVP® releases VWF from storage pools in the vascular endothelium thus giving rise to increases in circulating VWF and FVIII. It can be used in women with VWD although responses to DDAVP® may vary depending on the type of VWD [80]. It can also be effective in women with platelet disorders and carriers of FVIII deficiency. DDAVP® may also be used in most of the mild rare bleeding disorders due to its ability to act as a hemostatic bypassing agent enhancing thrombin generation.

Acute heavy menstrual bleeding requires coordinated rapid care to achieve control over heavy vaginal bleeding as it can be life-threatening. Heavy menstrual bleeding can be especially dangerous in some patients with severe inherited bleeding disorders such as type 3 VWD, Glanzmann's Thrombasthenia, or factor XIII (FXIII) deficiency and thus consideration may be given to suppress menarchal bleeding entirely in these patients. Close observation may also be a suitable alternative in some patients. An exchange with an expert gynecologist to discuss the risk-benefit of suppressing menarche would be optimal for select high-risk patients. Factors such as family bleeding patterns, patient compliance and distance from a treatment center should be considered in

Date and time of prescription	Nursing Time order taken	Time order faxed	Medical orders*
			Nursing: Diet (specify): Vital signs q 30 minutes x 2, q1hour x 2, q4hour if stable Advise if systolic blood pressure <90 mmHg or HR >120 bpm Start pad and tampon count using pictorial blood loss assessment chart (PBAC) Advise if pad changes more than 1 per hour are required Monitor In and outs [CS1] q 4 hours Consultation with haematology
			IV : RL or NS [CS2] Rate: 120 cc/hr
			Laboratory Tests: Before transfusion and/or hormone therapy draw the following tests (and keep a frozen plasma sample): Complete blood count, coagulation studies (APTT, INR), fibrinogen, ferritin and VWD profile (VWD:Ag, VWD:RCoF, FVIII:C)
			Medications: Conjugated oestrogens (Premarin) first dose STAT ____2.5 mg po qid or ____25 mg IV q 4–6 hours if patient does not tolerate po Tranexamic acid (Cyklokapron) first dose STAT ___ 25 mg/kg (max 1500 mg/dose) ___ mg po tid or ___ 10 mg/kg (max 600 mg/dose) ___ mg IV q8 hours Omit tranexamic acid if DIC, presence of venous or arterial thromboembolism, hemorrhage in closed space, presence of macroscopic hematuria or color blindness. Should be used for the shortest duration required to control bleeding in women with known thrombophilia. Metoclopromide (Maxeran) 0.1 mg/kg (max 10 mg) ____ mg po or IV, 30 to 60 minutes before each dose of conjugated oestrogens or Promethazine 25-50mg po or IV 30-60 minutes before each dose of conjugated oestrogens If metoclopromide ineffective: Odansetron (Zofran) 0.15 mg/kg (max 8 mg)___mg po or IV q 4hr (maximum 3 doses in 24hours) 30 to 60 minutes before each dose of conjugated oestrogens If Hb <100 g/L add: Ferrous sulfate 300 mg po bid Folic acid 5 mg [CS3] po qd

Fig. 3. Sample Care plan for Acute Menstrual Blood Loss.
Source: James AH et al. Eur J Obstet Gynecol Reprod Biol. 2011 Oct;158(2):124-34.

this decision. Patient education on the warning signs of excessive menstrual bleeding is imperative. Tragically Hjordis, the famous index case first described by Dr. Erik von Willebrand with severe VWD lived remotely and died from hemorrhage on her fourth menstrual period, at age 14.

A management algorithm for heavy menstrual bleeding should be readily available in most hospitals. It is very important that Hemophilia Treatment Centers work with emergency rooms in their region to alert staff to the presence of patients with severe bleeding disorders living nearby. The mainstay of treatment is a combination of high dose estrogens and tranexamic acid. An example care plan from Sainte-Justine University Hospital Center in Montreal (Canada) has been published in a review on the treatment of heavy menstrual bleeding [69] and is shown in Fig. 3. Such protocols can improve patient care by more effectively reducing bleeding thus decreasing the number of required surgical interventions and, in addition, prompting the physician to think about testing for an underlying bleeding disorder in appropriate patients [81].

5.2. Pregnancy

The management of women with inherited bleeding disorders in pregnancy is a challenge due to separate fetal and maternal considerations as well as the inconsistent nature of pregnancy's effect on hemostatic variables. It therefore requires a specialized distinct approach for each bleeding disorder and severity.

i) Antepartum management

A key goal of care is to make sure that all pregnant patients are iron replete throughout pregnancy and the postpartum period and ideally this process should be initiated before pregnancy. Optimally, pregnant women should have excellent iron stores with ferritin levels between 50 and 100 pmols; higher levels closer to 100 pmols may be more protective of iron losses in the event of postpartum hemorrhage but may be difficult to achieve. As iron deficiency has negative effects on the developing brain [82], attention to iron repletion in pregnancy is likely cost-effective across a life span of the newborn. Iron deficiency is the most common nutrient deficiency in the world affecting 2 billion individuals and 30–50% of pregnant women [83,84]. 'IRON MOM', initially a paper-based tool kit that has now gone digital (available as an app), has been developed for caregivers to assess, diagnose and manage iron deficiency in pregnancy. Iron deficiency may lead to acquired platelet dysfunction [44] and thus exacerbate bleeding risk during pregnancy and at the time of delivery.

Although antepartum bleeding is uncommon in VWD and other mild bleeding disorders, it can be common in rare bleeding disorders such as FX deficiency, hypofibrinogenemia, dysfibrinogenemia, and FXIII deficiency [7,85,86]. Miscarriage rates in these patients are also increased compared to the general population [87–97]. Bleeding can be life threatening in these patients and some must be considered for continuous hemostatic prophylaxis starting in the antepartum period such as in severe FXIII deficiency [98]. It is unclear whether women with VWD are at excessive risk for miscarriage and studies are required to address this issue. An ongoing multicenter Canadian study will help address this lack of data [99].

Levels of VWF and FVIII increase progressively in pregnancy reaching peak values in the late third trimester when hemostatic planning for delivery and regional anesthesia are carried out for women with VWD and carriers of Hemophilia A [100]. Those who start with lower levels typically correct less at term. While most VWF and FVIII levels in mild cases of VWD and most FVIII levels in hemophilia A carriers with mild FVIII deficiency will normalize in pregnancy, hemostatic coverage may be required for interventions occurring in the first and second trimester such as chorionic villus sampling or amniocentesis [101,102]. The other coagulation factors may also rise later in pregnancy except for factors II, V and IX which usually do not change and factor FXI is variable. FXIII tends to decrease during pregnancy [103].

ii) Peripartum management

Patients with VWD, are at risk for both primary (within 24 h of delivery) and secondary (> 24 h after delivery) post-partum hemorrhage. Five percent to 44% of women with VWD suffer from primary post-partum hemorrhage, and women who do not attain hemostatic correction by the time of delivery are at particular risk even with hemostatic coverage [104]. Twelve to 25% of women with VWD have secondary postpartum bleeding. These likely occur when VWF levels reach their baseline levels at 1 to 3 weeks following delivery [104,105]. Although the reported risk of primary postpartum hemorrhage in women with VWD is high, a population-based cohort data base suggested that the absolute risk of postpartum hemorrhage in the VWD population is still quite low 6% compared with 4% in the general population [106]. Regardless, this data supports an appropriate interventional approach for these women especially as these risk factors are so modifiable.

FVIII levels follow a similar trajectory to VWF in pregnancy and this means that women carriers of hemophilia A likely share a similar risk of postpartum bleeding although prospective studies are required to determine this risk. Typically, coagulation FIX and FXI do not increase significantly during pregnancy although there are a few reports of the factor levels increasing slightly or FXI decreasing slightly closer to term [23,103]. Therefore, the possible need for hemostatic coverage at the time of delivery should be anticipated in these women and should be assessed in the third trimester. Patients with FXIII deficiency may actually lower their levels in pregnancy and thus the need for hemostatic coverage must be determined.

Patients who normalize their hemostatic profile in the third trimester do not require hemostatic preparation for delivery. For the minority of women with VWD or Hemophilia A carrier status, who have inadequate levels of VWF and FVIII at term, DDAVP® or factor concentrates may be used [107] with or without tranexamic acid. Tranexamic acid alone could be considered in patients whose hemostatic profile remains marginal. Tranexamic acid prophylaxis seems to be safe and effective in women with inherited bleeding disorders and is often used alone or as an adjuvant to hemostatic therapy [108].

The cutoff factor level of 0.50 U/ml is typically used to determine if the patient requires hemostatic coverage or not. It is generally considered that patients who attain levels of VWF and FVIII > 0.50 U/ml do not require prophylaxis for delivery [109]. It remains unclear as to whether VWF and FVIII levels of 0.50 U/ml are sufficient to prevent postpartum hemorrhage although anecdotal evidence suggests that 0.50 U/ml is probably not enough considering that normal women attain physiologically VWF or FVIII levels of on average 3–4 x that at the time of delivery. The ideal hemostatic cutoff for delivery in women with VWD or hemophilia carriers is the focus of ongoing clinical trial (personal communication).

Patients with type 1 and some with type 2 whose levels of FVIII and VWF are < 0.50 U/ml and > 0.30 U/ml at term can usually be treated with DDAVP® and tranexamic acid [109–111]. In a case in which a previous elective DDAVP® trial was done when the woman was not pregnant, the results may be used to predict her response at delivery although an individual`s response to DDAVP® in pregnancy compared to the non-pregnant state has not been formally studied. Some patients with severe type 1 VWD may not respond to DDAVP® [112] especially those with low baseline levels (< 0.10 U/mL). Women with some forms of type 2 VWD may have an inadequate response to DDAVP® [113]. DDAVP® is relatively contraindicated in type 2B VWD due to the risk of platelet clumping and the potential for thrombotic complications although this risk is controversial [114]. It has been shown that patients with certain mutations associated with subtypes of VWD may predict the extent of factor level increases in pregnancy as well as determine the response to DDAVP®. This information, if available, could be used to know which pregnant patients will require VWF replacement therapy [111,115].

DDAVP® may be contraindicated for some women due to a prior history of unacceptable side-effects, in particular headaches, presyncope/syncope, hyponatremia and fluid retention. Thus, consideration for factor replacement (plasma derived or recombinant) must be given.

In addition to VWF concentrate, platelet transfusions have rarely been given for Type 2B VWD for peripartum prophylaxis [116,117]. Type 2B VWD can be associated with significant thrombocytopenia and the platelet count can worsen in pregnancy as VWF increases and as such may increase the patient`s bleeding propensity [118] although some of the drop may be due to platelet clumping. Women with type 3 VWD will require factor concentrate. Replacement guidelines for hemostatic therapy have been published in the USA [119] but given the paucity of high-quality well-designed trials in this area, guidance is drawn largely from expert opinion based on the non-pregnant state and thus practices vary greatly.

Appropriate hemostatic cutoffs for delivery for the rare bleeding disorders are even less clear and levels are extrapolated from non-pregnancy surgical data. Expert guides based on clinical observations are invaluable in the care of patients affected by rare Hereditary Bleeding Disorders. Considerations for peripartum prophylaxis should include the appropriate factor replacement for the specific diagnosis, factor level target, bleeding risk i.e. vaginal or cesarean section, the personal and family history which is especially important for those inherited disorders, such as FVII or FXI deficiency, in which the factor level does not correlate with the bleeding phenotype. It is important to be careful of over treating patients who require plasma for replacement during labor due to the risk of precipitating pulmonary edema. In the future, global assays of hemostasis (TEG, ROTEM) may have an especially important role to guide hemostatic therapy in these inherited bleeding disorders [120,121] especially in mild or rare types.

A detailed delivery plan should be established with input from an expert multidisciplinary team including recommendations regarding the site of delivery (i.e. specialized center or local hospital). This plan should address decisions for antepartum and peripartum hemostatic prophylaxis as well as treatments anticipated in the event of a postpartum hemorrhage and should be readily available in the patients file. A copy of the plan should also be given to the patient and to all members of the treating team.

Neuroaxial anesthesia has not been well studied in pregnancies of women with inherited bleeding disorders. Due to the rarity of epidural hematoma in the general population (approx. 1/million) prospective studies are unlikely feasible. The risk of epidural bleeds is reported to be 1/200,000 in pregnancy [122,123]. Patients with bleeding disorders are presumed to have a relatively higher risk of epidural hematoma (data extrapolated from thrombocytopenic patients) than those in the general population although the true absolute incidence of this complication in this patient group is not known. Regardless, caution should be exercised when offering regional or local anesthesia to women with inherited bleeding disorders especially those who have not corrected their hemostatic profile at term. One review looked at women with VWD requiring hemostatic prophylaxis for regional anesthesia. For patients with normal factor levels, there were no bleeding events, although the number of patients was small [124]. As a general rule,

alternatives to regional anesthesia should be considered in patients with persistently impaired hemostatic parameters in the 3rd trimester unless normalization of hemostasis can be ensured [125]. These options should be reviewed with an expert anesthesiologist and would be part of the multidisciplinary team delivery plan.

iii) Postpartum management

Practices to prevent and treat hemorrhage in the postpartum period vary widely. Active management of the 3rd stage of labor should be standard for women with inherited bleeding disorders [126]. In the event of a post-partum hemorrhage, the usual obstetrical hemostatic measures should be tried including tranexamic acid. Tranexamic acid has been shown to be effective in reducing bleeding and mortality in women without inherited bleeding disorders who have post-partum hemorrhage [127].

DDAVP® can be used for patients with type 1 or 2 VWD and hemophilia A carriers who have low factor levels. It can also be used for hereditary platelet dysfunction and could be tried for mild rare factor deficiencies including FXI deficiency.

Practices around DDAVP® utilization in pregnancy and postpartum hemorrhage are variable. Some completely avoid DDAVP® in pregnancy due to the risk of fluid overload and hyponatremia despite it being relatively safe [128]. Potential toxicity with DDAVP® could be exaggerated if given around the time of octostim administration so this should be avoided if possible. Some precautions to prevent side effects of DDAVP® include having the patient lie flat during the administration while monitoring blood pressure and heart rate, limiting the total fluid volume to 1 L over 12–24 hours after the dose of DDAVP®, giving saline if IV fluids are required, checking the sodium level and avoiding a repeat dose. Some experts endorse administrating DDAVP® after umbilical cord clamping to avoid hyponatremia in the fetus although clear evidence for this practice is lacking [10].

Some centers will prescribe tranexamic acid to all women with inherited bleeding disorders in the postpartum period to prevent secondary post-partum hemorrhage while some others treat only those identified at higher risk for hemorrhage and others recommend hormonal prophylaxis. There is a paucity of evidence to guide this choice. Giving a prescription of tranexamic acid to the patient at discharge with instructions for early use in the event that heavy vaginal bleeding starts is a suitable and safe option in low risk patients. Advising the patient to contact the treatment center in case of abnormal bleeding is also necessary. DDAVP® and hormonal options should also be considered in the event of delayed postpartum bleeding unresponsive to tranexamic acid.

5.3. Hemorrhagic ovarian cysts

Women with bleeding disorders may be at increased risk of hemorrhagic ovarian cysts and in some cases, these can be life threatening. There is no data on the exact incidence of this complication. In one study, patients with VWD were more likely to have simple ovarian cysts than the control group patients [7,60]. Biases towards more frequent imaging in patients with VWD presenting to the emergency room or gynecologists office may explain part of this reported increased risk. Management is mostly conservative. Acute management consists of supportive therapy, DDAVP®, tranexamic acid, transfusion therapy and hormonal therapy to suppress ovulation. This is most effectively done using high dose estrogens, combined oral contraceptive pills and Depo-Provera. Management is best orchestrated by a gynecologist in conjunction with a hematologist who can guide hormonal and replacement therapies, respectively. Surgical management is used only as a last resort if hemostatic conservative management fails and perioperative hemostatic coverage is essential.

6. Conclusion

In this dawning era of patient informed care, we know that the absolute best investment of our resources is in providing superb antenatal, perinatal and post-partum care to reduce the risk of illness and death of mothers. The high mortality and morbidity of women with inherited bleeding disorders has had devastating consequences for women and their families for millennia and yet have only recently begun to receive attention in the medical and public spotlight. Restoring quality of life to women with excessive bleeding from menses is now a priority. Publications on these issues have increased steadily due to physician and research interest in this area. Many studies are making a meaningful impact in providing best care to these women and we are gradually filling the gaps where there is a lack of evidence-based recommendations.

Public awareness campaigns, physician education and better available standardized bleeding assessment tools have helped improve screening leading to a progressively increasing number of patients identified.

Today's health- care practitioners require appropriate clinical knowledge and skills to manage women with inherited bleeding disorders and as such work has been done to integrate teaching into medical curricula and in residency training programs [129]. It is our hope that our combined efforts will contribute to improved care for women with inherited bleeding disorders. Ideally many bleeding episodes will be prevented and if they do occur, they will be managed optimally to give these women the best quality of life.

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