

# Preoperative diagnosis and management of inherited bleeding disorders in female adolescents and adults

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Although inherited bleeding disorders (IBDs) affect both females and males, this review of the preoperative diagnosis and management of IBDs focuses on genetic and gynecologic screening, diagnosis and management of affected and carrier females. A PubMed literature search was conducted, and the peer-reviewed literature on IBDs was evaluated and summarized. Best-practice considerations for screening, diagnosis and management of IBDs in female adolescents and adults, with GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) evidence level and ranking of recommendation strength, are presented. Health care providers need to increase their recognition of and support for female adolescents and adults with IBDs. Improved access to counselling, screening, testing and hemostatic management is also required. Patients should be educated and encouraged to report abnormal bleeding symptoms to their health care provider when they have a concern. It is hoped that this review of preoperative IBD diagnosis and management will enhance access to women-centred care to increase patients' understanding of IBDs and decrease their risk of IBD-related morbidity and mortality.

Même si les troubles héréditaires de la coagulation affectent les femmes et les hommes, la présente revue sur leur diagnostic et leur prise en charge en contexte préopératoire s'intéresse au dépistage génétique et gynécologique, au diagnostic et à la prise en charge des femmes atteintes et porteuses. Nous avons interrogé la base de données PubMed et nous avons évalué et résumé les articles révisés par des pairs au sujet des troubles héréditaires de la coagulation. Nous présentons un aperçu des pratiques optimales en matière de dépistage et de diagnostic des troubles héréditaires de la coagulation chez les adolescentes et les femmes au moyen du système GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) qui évalue la qualité des données probantes et la force des recommandations. Les professionnels de la santé doivent mieux reconnaître les troubles héréditaires de la coagulation chez les adolescentes et les femmes afin de mieux soutenir cette population. Un meilleur accès au counseling, au dépistage, aux tests et à la prise en charge de l'hémostase s'impose également. Il faut renseigner les patientes et les encourager à informer leur médecin de tout saignement anormal qui les inquiète. Nous espérons que cette revue du diagnostic et de la prise en charge préopératoires des troubles héréditaires de la coagulation facilitera l'accès à des soins centrés sur les femmes et aidera ces dernières à être mieux renseignées afin de réduire le risque de morbidité et de mortalité associé aux troubles héréditaires de la coagulation.

**T**he pathway to high-quality and safe care for people with inherited bleeding disorders (IBDs) continues to be challenging. Patients at risk may encounter obstacles in accessing appropriately resourced, high-quality comprehensive care centres for innovative evidence-based treatment.<sup>1</sup> The IBDs that affect female surgical care include inherited von Willebrand disease (vWD) and X-linked hemophilia A and B carrier status, as well as rare platelet disorders.

Focused genetic and hematologic education related to IBDs is required for the surgical health care provider. Enhanced medical and nursing training curricula and public awareness are necessary as well.<sup>2,3</sup>

Although IBDs affect both female and male patients, this review focuses on preoperative surgical screening, diagnosis and management of affected or carrier females. The review provides an evidence-based diagnostic and genetic classification and management pathway to help provide a framework for reducing IBD morbidity in affected adolescent and adult females undergoing scheduled surgical procedures.

## METHODS

A scoping review methodology was used. The review was focused primarily on IBDs in adolescent and adult females and pregnant people with vWD, hemophilia A and B carrier status, and inherited platelet disorders. Keywords, report titles, peer-reviewed articles with reference review and author names were used in the search strategy. PubMed was searched for relevant articles in English with the keywords “von Willebrand disease,” “hemophilia A,” “hemophilia B,” “inherited platelet disorders,” “screening criteria,” “diagnostic criteria,” “genetic testing,” “laboratory testing,” “major surgery,” “minor surgery,” “pregnancy,” “menorrhagia” and “prophylaxis.” The scoping review identified adequate data sources for this evidence-based focused review of the topic.

## PRESENT HEALTH CARE STATUS OF FEMALES WITH INHERITED BLEEDING DISORDERS

The impact of IBDs is substantial. The clinical issues of bleeding severity, determination of the patient’s individual risk related to surgery and pregnancy, disease transmission, testing and reproductive decisions contribute to health-related quality of life.<sup>4-17</sup> Compared to females without IBDs, those with IBDs have lower values for bleeding control, vitality, and physical and social functioning, and increased pain (joint bleeding/heavy menstrual bleeding) and psychosocial problems (guilt, anxiety, depression, work and school absenteeism, isolation and difficult social relationships).<sup>4-17</sup> Women’s occupational opportunities are substantially affected, related to the person’s disease severity and, in the case of familial hemophilia, the potential need to undertake a role as caregiver.<sup>4-17</sup> Patient access to specialist care is commonly reported as an obstacle.<sup>4-17</sup>

Knowledge translation regarding male hemophilia A and hemophilia B outcomes is important for informed-consent counselling of female hemophilia carriers. Both hemophilia A and hemophilia B have transitioned from a disease of childhood to one of adulthood. Life expectancy has increased from 11 years in the mid-1900s to the present 55–63 years owing to management with coagulation factor concentrates. There are long-term clinical concerns associated with hemophilia outcomes, including chronic viral infections with liver disease, joint impairment with bone disease, cardiovascular disease, cancers, chronic kidney disease, covert cerebral microbleeds, impaired sexuality and development of immune factor inhibitors.<sup>18</sup>

## PRIMARY RISK SCREENING IN FEMALE ADOLESCENTS AND ADULTS WITH AN ABNORMAL BLEEDING HISTORY

Health care providers need to increase their recognition of and support for female adolescents and adults with

IBDs. Improved access to counselling, screening, testing and hemostatic management is also required. Patients should be educated and encouraged to report abnormal bleeding symptoms to their health care provider when they have a concern.

The genetic impact, definition and coagulation testing factors of IBDs affecting female adolescents and adults are summarized in Table 1.<sup>2,19-32</sup> The coagulation cascade summarizes the factors and their interactions to achieve hemostasis–thrombosis balance<sup>33</sup> (Figure 1).

Menorrhagia is the most common symptom reported by female adolescents and adults with IBDs. The clinical descriptions that indicate serious menorrhagia are soaking through menstrual pads or tampons within 1 hour, soaking through bedclothes, decreased ferritin level and anemia (microcytic; hemoglobin level < 10 g/dL) and, as an objective measurement, a score less than 100 on a pictorial bleeding assessment chart (PBAC).<sup>34</sup>

Health care providers must consider a bleeding disorder in adolescent females with bleeding problems, as 50% of patients have some form of coagulopathy.<sup>35,36</sup> Many females diagnosed with an IBD as an adult will have been missed as an adolescent.

## Evaluation

Evaluation of females with an IBD consists of the following elements:<sup>22,23</sup>

- History and physical examination
  - ♦ Current clinical status (characterize bleeding phenotype, complete a bleeding assessment tool)
  - ♦ History of excessive bleeding (determine whether history is lifelong)
  - ♦ History of joint pain/swelling (identify undiagnosed hemarthrosis)
  - ♦ History of chronic diseases (identify nongenetic causes)
  - ♦ Reproductive history (assess fertility)
- Family history and pedigree
  - ♦ Family history from reliable relatives (determine inheritance patterns)
  - ♦ Laboratory results of affected relatives (determine severity in males)
- Verbal review of the use of nonwarfarin and over-the-counter medications, as certain agents have an associated bleeding risk (Table 2).<sup>33</sup>

The screening criteria used to identify a possible diagnosis of IBD are as follows:<sup>34,35</sup>

  - Adolescents
    - ♦ Menses lasting longer than 7 days, bleeding through a pad or tampon in 1 hour, clots greater than 3 cm in diameter, or bleeding that results in anemia or low iron status
    - ♦ Bleeding requiring a transfusion
    - ♦ Unmanageable heavy menstrual bleeding

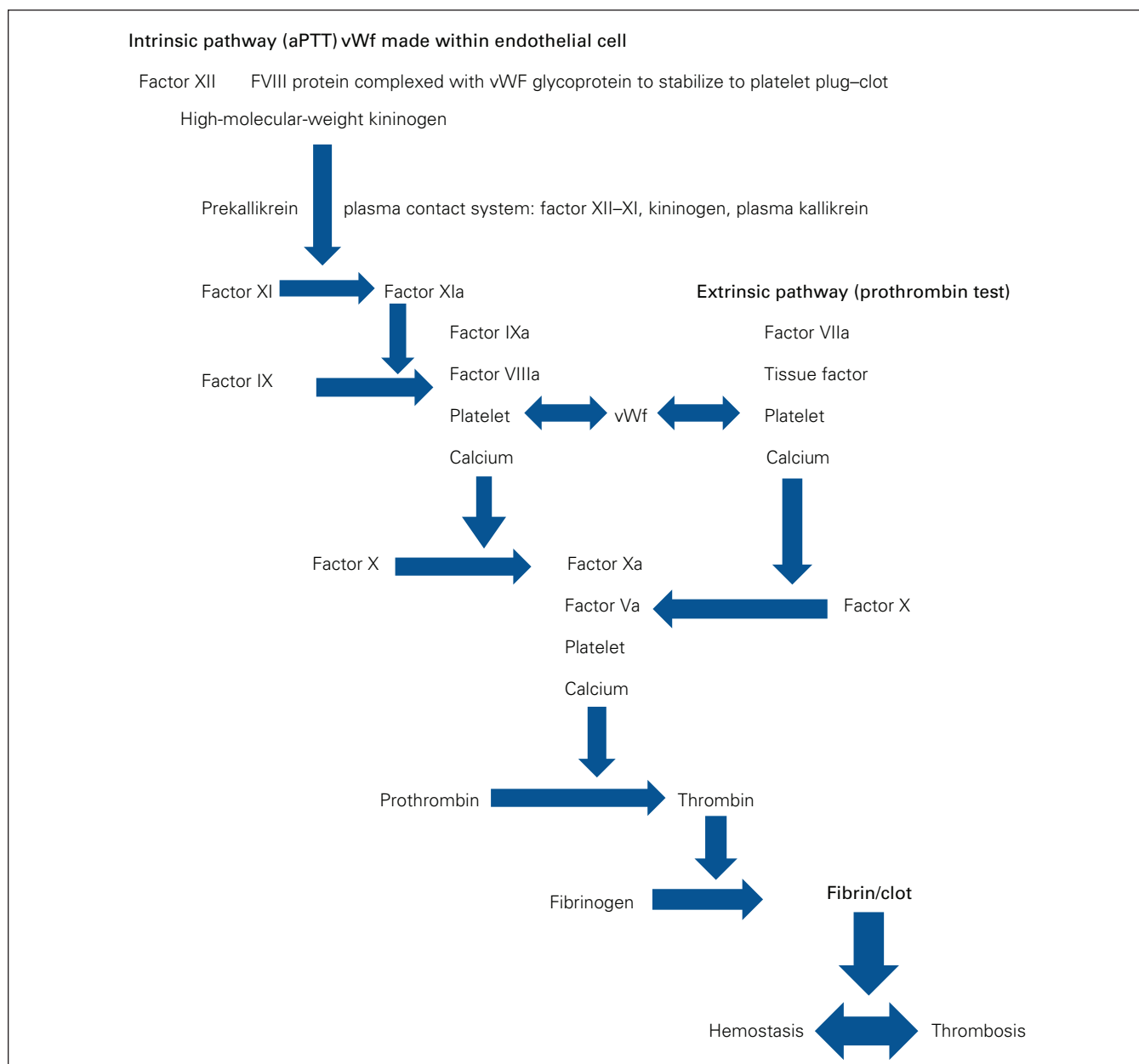
**Table 1. Genetic impact, definition and coagulation testing of inherited bleeding disorders**

| Disorder   | Genetic impact  | Definition  | Coagulation testing  |
|--|---|---|--|
| von Willebrand disease <sup>2,19,20</sup>        | <ul style="list-style-type: none"> <li>vWF gene / 12p (13.31)</li> <li>Autosomal dominant: types 1, 2A, 2B, 2M</li> <li>Autosomal recessive: types 2N, 3</li> <li>In pregnancy:                             <ul style="list-style-type: none"> <li>Type 1: vWF/factor VIII level normal</li> <li>Type 2: vWF/factor VIII level increased</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>Prevalence 1300/100 000</li> <li>Mucocutaneous bleeding</li> <li>Family history</li> <li>vWF deficiency</li> </ul>   | <ul style="list-style-type: none"> <li>Low vWF antigen level and functional assay result</li> <li>Prolonged aPTT</li> <li>Prolonged bleeding time or closure time</li> <li>Low factor VIII level</li> <li>Quantitative deficiency: types 1 and 3</li> <li>Qualitative deficiency: types 2, 2A, 2B, 2M, 2N</li> </ul> |
| Hemophilia A <sup>21-23</sup>                    | <ul style="list-style-type: none"> <li>X-linked recessive (male) factor VIII</li> <li>F8; Xq28</li> <li>Severe-moderate in 70% of cases</li> <li>Mild in 30% of cases</li> <li>Female carrier is heterozygote</li> </ul>  | <ul style="list-style-type: none"> <li>Prevalence in males 17/100 000 (1/5000)</li> <li>Factor VIII level &lt; 2% of normal</li> <li>Factor VII level 2%–25% of normal</li> <li>In about 50% of cases</li> </ul>  | <ul style="list-style-type: none"> <li>Prolonged aPTT</li> <li>Low factor VIII level</li> <li>aPTT usually low normal</li> </ul>   |
| Hemophilia B <sup>24-26</sup>                    | <ul style="list-style-type: none"> <li>X-linked recessive (male) factor IX</li> <li>F9; Xq27</li> <li>Severe-moderate in 70% of cases</li> <li>Mild in 30% of cases</li> <li>Female carrier is heterozygote</li> </ul>  | <ul style="list-style-type: none"> <li>Prevalence in males 4/100 000 (1/30 000)</li> <li>Factor IX level &lt; 2% of normal</li> <li>Factor IX level 2%–25% of normal</li> <li>In about 50% of cases</li> </ul>  | <ul style="list-style-type: none"> <li>Low factor IX level</li> <li>Prolonged aPTT</li> <li>aPTT usually normal, low factor IX level</li> </ul>  |
| Factor XII deficiency <sup>27</sup>              | —   | —   | <ul style="list-style-type: none"> <li>Low factor XII level</li> <li>Prolonged aPTT</li> </ul>   |
| Factor XIII deficiency <sup>28</sup>             | Autosomal recessive   | <ul style="list-style-type: none"> <li>Prevalence 1/2 000 000–1/5 000 000</li> <li>Hemorrhagic diathesis</li> <li>Habitual abortion</li> <li>Defective wound healing</li> </ul>   | <ul style="list-style-type: none"> <li>Low factor XIII level</li> <li>aPTT and INR normal</li> </ul>   |
| Inherited platelet disorders <sup>29-31</sup>    | <ul style="list-style-type: none"> <li>Individually rare clinical heterogeneity</li> <li>Receptor defects</li> <li>Autosomal recessive</li> <li>Other platelet defects</li> <li>Autosomal dominant</li> </ul>   | <ul style="list-style-type: none"> <li>Prevalence of Bernard–Soulier syndrome and Glanzmann thrombasthenia 1/1 000 000</li> <li>Decreased or absent platelet surface receptors</li> <li>6 conditions:                             <ul style="list-style-type: none"> <li>Bernard–Soulier syndrome</li> <li>Glanzmann thrombasthenia</li> <li>Platelet type von Willebrand</li> <li>ADP receptor</li> <li>Thromboxane A2 receptor</li> <li>Glycoprotein VI deficiency</li> </ul> </li> <li>Aberrant secretion (impaired adherence to vascular endothelium) or altered signalling between platelets (impairing aggregation with other platelets)</li> </ul> | <ul style="list-style-type: none"> <li>Platelet count normal</li> <li>Prolonged bleeding time or closure time</li> <li>Abnormal results of specific platelet function assay</li> <li>Platelet function testing is not well standardized</li> </ul>   |
| Rare coagulation factor deficiencies             | <ul style="list-style-type: none"> <li>Autosomal recessive</li> <li>Autosomal recessive</li> <li>Autosomal recessive</li> <li>Autosomal recessive</li> </ul>  | <ul style="list-style-type: none"> <li>Factor VII (chromosome 13q34)</li> <li>Factor X (chromosome 13q34)</li> <li>Factor V (chromosome 1q24.2)</li> <li>Factor II (chromosome 11p11-p12)</li> </ul>  | <ul style="list-style-type: none"> <li>Low fibrinogen level</li> <li>Deficiency levels of specific factor(s)</li> </ul>  |
| $\alpha_2$ -antiplasmin deficiency <sup>32</sup> | Rare, but prevalence increased with consanguinity   |   | <ul style="list-style-type: none"> <li>Low <math>\alpha_2</math>-antiplasmin level</li> <li>aPTT and INR normal</li> </ul>   |

ADP = adenosine diphosphate; aPTT = activated partial thromboplastin time; INR = International Normalized Ratio; vWF = von Willebrand factor.

- ◆ Prolonged bleeding from small wounds lasting more than 15 minutes or recurrent bleeding after 7 days
- Adults: the above criteria as well as the following:
  - ◆ History of heavy or prolonged bleeding after a procedure or surgical intervention (e.g., tooth extraction, surgery, delivery)
  - ◆ Two or more of the following conditions: epistaxis once or twice per month, epistaxis lasting more than 10 minutes, frequently bleeding gums or family history of bleeding symptoms
  - ◆ Unexpected postsurgical bleeding, history of hemorrhagic ovarian or corpus luteum cyst

- ◆ Failure of response to conventional hormonal management of menorrhagia (combined estrogen–progesterone or progesterone alone).  
Validated tools are available for clinical bleeding history scoring, including a bleeding assessment tool (BAT) and a pictorial scoring system for pads and tampons (PBAC) used during bleeding episodes.<sup>36-40</sup> The ISTH-BAT (International Society on Thrombosis and Haemostasis – Bleeding Assessment Tool) comprises 14 categories for assessing bleeding symptoms retrospectively; a high bleeding score is associated with the presence of an IBD.<sup>37,38</sup> The PBAC is a prospective scoring system



**Fig. 1.** Traditional coagulation cascade model.<sup>33</sup> aPTT = activated partial thromboplastin time; vWF = von Willebrand factor.

developed as a semiquantitative evaluation of menstrual blood loss that considers the number of sanitary products used, the degree to which these products are soiled with blood, the number and size of blood clots passed, and the number of flooding episodes.<sup>39,40</sup> These tools provide useful methods for establishing the amount of bleeding, which can then be compared after therapy initiation.

#### *Hematology and laboratory studies*

Hematology screening of plasma should include the following elements:<sup>33–35</sup>

- Complete blood count

- Prothrombin time
- Activated partial thromboplastin time
- Factor VIII (FVIII) level decrease:
  - ◆ vWD profile (rule out vWD)
  - ◆ Factor V level (rule out factor V and FVIII deficiency)
  - ◆ FVIII binding to von Willebrand factor (vWF) (rule out vWD type 2N)
  - ◆ FVIII inhibitor (evaluate for possible acquired hemophilia)
- Factor IX (FIX) level decrease: factor II, factor VII, factor X (rule out genetic or acquired combined vitamin K–dependent clotting factor deficiency)
- FIX inhibitor (evaluate for possible acquired hemophilia)

**Table 2. Medications and over-the-counter medicines that entail a risk of increased bleeding<sup>33</sup>**

| Class; agent                                     | Mechanism  |
|--|--|
| <b>Antiplatelet drugs</b>                        |  |
| Acetylsalicylic acid                             | Inhibition of COX-1 and COX-2/thrombin generation  |
| Clopidogrel/ticlopidine                          | Inhibition of P2Y12 receptor on platelet surface   |
| Dipyridamole                                     | Blocks cellular uptake of adenosine with antiplatelet due to extracellular adenosine                           |
| NSAIDs   | Block COX-1 and COX-2  |
| Unfractionated heparin                           | Thrombin inactivation via antithrombin III binding sites   |
| Low-molecular-weight heparin (multiple products) | Thrombin inactivation via antithrombin III binding sites   |
| Fondaparinux                                     | Inhibition of thrombin generation  |
| <b>Direct thrombin inhibitors</b>                |  |
| Argatroban                                       | Reversible and direct inhibition of circulating and fibrin-bound thrombin                                      |
| Bivalirudin                                      |  |
| Hirudin  |  |
| Lepirudin  |  |
| Ancrod (purified snake venom protein)            | Defibrinogenation  |
| <b>Fibrinolytics</b>                             |  |
| Anistreplase                                     | Convert plasminogen to plasmin (fibrinolytic)  |
| Alteplase  |  |
| Retepase   |  |
| Tenecteplase                                     |  |
| Streptokinase                                    |  |
| Urokinase  |  |
| Drotrecogin alfa                                 | Vitamin K–dependent antithrombotic serine protease that directly inhibits factors Va and VIIIa                 |
| <b>Glycoprotein IIb/IIIa inhibitors</b>          |  |
| Abciximab  | Inhibition of platelet aggregation by binding of soluble fibrinogen to platelet receptor glycoprotein IIb/IIIa |
| Eptifibatide                                     |  |
| Tirofiban  |  |
| <b>Herbal medicines</b>                          |  |
| Anise  | Potential for thrombocytopenia   |
| Garlic   |  |
| Ginger   |  |
| Ginseng  |  |
| Ginkgo biloba                                    |  |
| Feverfew   |  |
| Herbal Plus                                      |  |

NSAID = nonsteroidal anti-inflammatory drug.

- von Willebrand panel (vWF activity–ristocetin cofactor test, vWF antigen level, FVIII level)
- Fibrinogen level
- Possible platelet function and/or aggregation studies, and thyroid function testing if the above screening gives normal results (normal platelet count 150–450 000 × 10<sup>9</sup>/L; normal values in Alberta: thyroid-stimulating hormone level 0.20–6.50 mIU/L, free T<sub>4</sub> level 10.0–25.0 pmol/L, free T<sub>3</sub> level [age ≥ 18 yr] 3.0–6.5 pmol/L)
- A hematology consultation may be required based on the laboratory screening results.

**Additional genetic studies after identification of primary etiology<sup>20,23,26</sup>**

- Paternity testing (rule out nonpaternity)
- Karyotype with high resolution of X (identify X chromosome abnormality)
- Sequencing of FVIII and FIX (identify point mutations)
- Multiplex ligation-dependent probe amplification (identify gene deletion or duplication)
- X chromosome inactivation studies (identify non-random inactivation).

**COMMON ETIOLOGIES AND DIAGNOSES IDENTIFIED IN FEMALES WITH INHERITED BLEEDING DISORDERS**

*von Willebrand disease<sup>2,19,20,41–44</sup>*

von Willebrand disease is the single most common IBD, with a laboratory risk-defined prevalence of 1% and a symptomatic prevalence of 0.1%. Autosomal dominant and recessive inheritance patterns are dependent on the vWD classification (Table 1).

The classical vWD triad association consists of mucocutaneous bleeding, family history of bleeding and a laboratory finding of a vWF deficiency. Directed questioning for pregnancy-related bleeding, epistaxis and heavy menstrual periods should be considered. The most commonly reported symptoms are heavy menstrual bleeding (75%–100% of patients), excessive bruising (60%–80%), oropharyngeal bleeding (64%), epistaxis (56%) and bleeding after dental surgery (24%–26%).<sup>44</sup>

In vWD, the bleeding tendency is due primarily to the inherited deficiency or dysfunction of the multimeric glycoprotein vWF, causing abnormal platelet–vessel wall interactions and defective formation of the platelet plug (primary hemostasis).

**Diagnosis**

There are pre-analytical variables that can affect the result of screening for an increased vWF level, such as delays in transportation or processing, estrogen level, pregnancy, physical or mental stress, and other medical conditions. Testing is required to evaluate quantitative and qualitative “diagnostic” results based on specific laboratory controls. The screening and diagnostic tests are prothrombin time, activated partial thromboplastin time, FVIII coagulant activity, ristocetin cofactor activity and vWF antigen concentration.<sup>2,19,20,41,42</sup>

Pregnancy is a prothrombotic physiologic event, and the hyperestrogen environment can increase vWF and FVIII levels by up to 300%–400%. These physiologic changes may minimize potential bleeding events, but pregnant people with vWD still have an increased risk for peripartum hemorrhage and the need for red cell transfusion. In addition, there is an increased risk of recurrent miscarriage.<sup>43</sup>

### *X-linked hemophilia A and B carrier status*

Hemophilia is an X-linked IBD, and females can be mutation carriers with variable levels of FVIII (hemophilia A) or FIX (hemophilia B). Female hemophilia carriers can be classified as obligate (daughters of affected male, women with > 1 affected son, women with 1 affected son and an affected brother or uncle) or possible (women with 1 affected son and no family history, daughters of an obligate carrier and woman with a maternal family history of hemophilia). A de novo germ cell X chromosome mutation is found in 30%–50% of newborn boys with hemophilia<sup>21–26,45–47</sup> (Table 1).

There are important characteristic differences between hemophilia A and B, such as hemostatic functional impact (cofactor in hemophilia A, enzyme in hemophilia B), genetic variant impact (null variant in 80% of cases of hemophilia A, missense variant in > 60% of hemophilia B cases) and risk of development of severe treatment-related inhibition of coagulation (in 35%–40% of cases of hemophilia A and 4%–5% of cases of hemophilia B).<sup>46</sup>

Genetic mechanisms explain most of the reported clinical variability. Possible causes of FVIII and FIX deficiency in women and girls are<sup>23,26,48–51</sup>

- Homozygosity (2 identical hemophilia alleles) by consanguinity, chance or de novo mutation(s)
- Compound heterozygosity (2 different hemophilia alleles) due to unrelated hemophilia families, de novo second mutation or 2 de novo mutations
- Hemizygoty (1 hemophilia allele and 1 normal allele) by single X chromosome 45,X/46,XY mosaicism with complete androgen insensitivity or complete gonadal dysgenesis, or X chromosome deletion of the *FVIII* or *FIX* gene
- Heterozygosity (1 hemophilia allele, 1 normal allele) by inheritance in hemophilia-affected family, or 1 new mutation followed by skewed X inactivation (unknown or random), preferential X inactivation due to X chromosome abnormality, cell viability disorder or specific allele of the X-inactive-specific transcript gene, or other inherited skewed X inactivation
- Other genetic causes: vWD, particularly type 2N \*autosomal recessive or dominant; factor V and FVIII deficiency (autosomal recessive); combined vitamin K-dependent clotting factor (II, VII, IX, XI) deficiency (autosomal recessive)
- Nongenetic cause: acquired hemophilia due to FVIII or FIX inhibitors, or vitamin K deficiency.

### **Diagnosis**

Female hemophilia A carriers have an FVIII deficiency, mild in 94% of cases, moderate in 3% and severe in 3%. The circulating plasma FVIII concentration observed in hemophilia A carriers ranges from normal to levels close to those of males with hemophilia, with a median level of 55% of normal (range 4%–136%).<sup>52</sup>

Female hemophilia B carriers have an FIX deficiency. The median FIX level is 45% of normal (range 19%–114%); 30% of patients have levels less than 40% of normal. The data for hemophilia B carrier morbidity are limited compared to those for hemophilia A carrier status.<sup>25</sup>

A new nomenclature for female hemophilia carriers aimed at improving diagnosis and management has been defined.<sup>53</sup> It distinguishes 5 clinically relevant categories: women/girls with mild, moderate or severe hemophilia (FVIII/FIX level > 0.05 IU/mL and < 0.40 IU/mL, 0.01–0.05 IU/mL and < 0.01 IU/mL, respectively) and symptomatic and asymptomatic hemophilia carrier status (FVIII/FIX level ≥ 0.40 IU/mL with and without a bleeding phenotype, respectively). With the new nomenclature, women attending US hemophilia treatment centres were identified as having mild (FVIII 16.0%, FIX 23.7%), moderate (FVIII 1.8%, FIX 0.86%) or severe (FVIII 0.49%, FIX 0.42%) hemophilia.<sup>23</sup> The proportion of women receiving hemophilia treatment in each category was 17.8%, 1.4% and 0.5%, respectively.

### *Inherited platelet disorders*

Inherited platelet disorders consist of a broad spectrum of medical conditions that include quantitative platelet disorders, which can present as increased or decreased platelet numbers, and qualitative platelet disorders, which affect platelet function. Inherited functional platelet disorders are rare, are commonly autosomal recessive and present usually in consanguineous populations<sup>29–31,54–57</sup> (Table 1). A history of mucocutaneous bleeding or periprocedural hemorrhage with no other secondary etiology or family history should raise clinical suspicion of an inherited platelet disorder.

An important distinction is that acquired disorders of platelet function are more common than inherited disorders. Antiplatelet drugs are the most common etiology of acquired disorders. Clinical conditions associated with acquired platelet dysfunction are uremia, hepatic cirrhosis, myeloma, polycythemia vera and essential thrombocythemia.<sup>58</sup>

### **Diagnosis**

The diagnosis is challenging and commonly delayed. The defects in platelet aggregation and activation can be from platelet receptors, platelet signalling, platelet granule release, platelet cytoskeletal remodelling or platelet hematopoiesis. Molecular studies have identified up to 40 genes as being causative of inherited thrombocytopenia, but in 50% of cases, no genetic basis has been identified.<sup>31</sup> Whole blood electronic counters are used to evaluate platelet count and size, and a blood smear (with or without staining technology) is also required. For platelet function assessment, the classic testing, such as aggregometry, secretion assays, flow cytometry, Western blotting and electron microscopy, is time consuming and expensive, and interpretation of the results is complex.<sup>31</sup>

Quantitative platelet disorders associated with an inherited thrombocytopenia etiology are a large heterogeneous group of rare platelet disorders characterized by low platelet count, leading to bleeding and syndromic and systemic manifestations. The prevalence is estimated at 1 per 100 000, but many patients are undiagnosed.<sup>30</sup>

Inherited qualitative (functional) platelet disorders affect normal platelet function at different stages of initial hemostasis: adhesion (Bernard–Soulier syndrome), activation, granule secretion (Hermansky–Pudlak syndrome, Quebec platelet disorder), signal transduction, aggregation for platelet thrombus formation (Glanzmann thrombasthenia) and coagulation factor activation (Scott syndrome).<sup>30</sup>

**COAGULATION CASCADE AND THE DRUGS, MEDICATIONS AND BLOOD PRODUCTS USED IN MANAGEMENT**

Understanding the coagulation cascade is important for IBD care in order to implement individualized manage-

ment choices. Figure 1 summarizes the intrinsic and extrinsic systems that result in the development of fibrin-based clotting, with normal balance between the thrombosis and hemostasis states.

Female adolescents and adults with IBDs have a spectrum of bleeding risk based on the genetics and physiology of the coagulation factor imbalance. The deficiency factors include vWF, coagulation factors VIII, IX, XI, VII, XIII and V, and platelet abnormalities. These deficient coagulation factors can be harvested from donated human plasma sources, through technology for recombinant products and with specific HLA platelet selection techniques.<sup>2,33,59</sup>

The products used for deficiency replacement are as follows: FVIII, recombinant FVIII concentrate; FIX, recombinant FIX concentrate; plasma-derived factors V, VII, XI, XIII concentrate; fresh frozen plasma (can be used if factor XI concentrate is unavailable, as it contains all the coagulation factors); vWF concentrate; tranexamic acid; and desmopressin (Table 3).<sup>2,59</sup>

**Table 3. Plasma concentrates and drug products used for management of inherited bleeding disorders<sup>2,59</sup>**

| Concentrate drug product                                    | Important effects   | Why used  | How used  |
|---|---|---|---|
| Factor VIII deficiency: recombinant factor VIII concentrate | —   | Genetic deficiency  | Intravenous transfusion   |
| Factor IX deficiency: recombinant factor IX concentrate     |   |   |   |
| Factor V deficiency: factor concentrate                     |   |   |   |
| Factor VII deficiency                                       |   |   |   |
| Factor XIII deficiency                                      |   |   |   |
| Factor XI deficiency: plasma-derived factor XI concentrate* |   |   |   |
| Tranexamic acid   | <ul style="list-style-type: none"> <li>• Lysine analogue that binds plasmin, preventing it from adhering to fibrin and thus preventing clot breakdown</li> <li>• Adverse effects: dizziness and nausea/thrombosis may occur with other thrombotic risk factors</li> </ul>   | Inhibits fibrinolysis   | <ul style="list-style-type: none"> <li>• Administered intravenously or orally, or suspended in solution for topical or mouthwash use</li> <li>• 1000–1300 mg orally or 1000 mg intravenously 3 times per day</li> <li>• Weight-based dosing 10 mg/kg 3 times per day</li> </ul>   |
| Desmopressin  | <ul style="list-style-type: none"> <li>• Vasopressin derivative that releases stores of vWF and factor VIII from endothelial cells; can elevate plasma levels of vWF and factor VIII three- to fivefold</li> <li>• Adverse effects: has antidiuretic hormone activity, so fluid restriction is recommended</li> </ul> | <ul style="list-style-type: none"> <li>• Used primarily for vWD type 1, as endothelial cells must produce normal molecules</li> <li>• Use in type 2 minor bleeding is valid</li> </ul>  | <ul style="list-style-type: none"> <li>• Administered intravenously or subcutaneously (0.3 µg/kg) for clinic or hospital-based use, or as nasal spray by outpatients (common use for heavy bleeding)</li> <li>• A test dose to determine the size and duration of the response is recommended, as the 2 responses may vary substantially; response frequently declines with repeated use at intervals &lt; 24–48 h</li> </ul> |
| vWF concentrate†  | —   | <ul style="list-style-type: none"> <li>• vWF-containing concentrate with high-molecular-weight vWF multimers is used for treatment if desmopressin is contraindicated or if response is likely to be inadequate</li> <li>• Has second role in hemostasis: to bind to factor VIII and protect it from premature clearance and degradation</li> </ul> | Intravenous transfusion   |

vWD = von Willebrand disease; vWF = von Willebrand factor.

\*If factor XI concentrate is not available, fresh frozen plasma can be used, as it has all the coagulation factors.

†The size of vWF multimers and therefore their activity are regulated by the plasma enzyme ADAMTS13, which cleaves vWF in the A2 domain.

**Table 4. Summary of traditional antithrombotic therapies for use in elective surgical management of inherited bleeding disorders\***

| Therapy  | Mechanism   | Delivery route              | Indication   |
|--|---|-----------------------------|--|
| <b>Anticoagulant</b>   |   |                             |  |
| Warfarin, phenprocoumon  | Inhibition of vitamin K-dependent carboxylation of factors II, VII, IX, X | Oral                        | Prevention and treatment of venous and arterial thrombosis/thromboembolism   |
| Unfractionated heparin, low-molecular-weight heparin   | Activation of antithrombin  | Intravenous or subcutaneous | Prevention and treatment of venous and arterial thrombosis/thromboembolism   |
| Direct oral anticoagulants (direct thrombin or factor Xa inhibitors)   | Inhibition of thrombin or factor Xa                                       | Oral                        | Prevention and treatment of venous and arterial thrombosis/thromboembolism   |
| <b>Antiplatelet</b>  |   |                             |  |
| Acetylsalicylic acid   | Inhibition of cyclooxygenase  | Oral                        | Secondary prophylaxis of infarction or ischemic stroke   |
| Continuing acetylsalicylic acid before elective surgery  | Inhibition of cyclooxygenase  | Oral                        | <ul style="list-style-type: none"> <li>• Major bleed RR 1.31 (95% CI 1.15–1.50)</li> <li>• Stroke RR 1.00 (NS)</li> <li>• Major thromboembolic event RR 0.75 (95% CI 0.59–0.95)</li> <li>• Myocardial infarction RR 1.05 (NS)</li> </ul> |
| Thienopyridine   | P2Y receptor antagonist   | Oral                        | Secondary prophylaxis of infarction or ischemic stroke   |
| CI = confidence interval; NS = nonsignificant; RR = relative risk.<br>*Adapted from Mailer and colleagues <sup>61</sup> and Alkhalil and colleagues. <sup>62</sup> |   |                             |  |

Traditional antithrombotic therapies (anticoagulation, antiplatelet) may be required in females with IBDs needing other surgical and medical treatments.<sup>2,55–57,59–63</sup> The available anticoagulation drugs are used to reduce the risk of thrombosis but result in a concomitantly increased risk of bleeding (Table 4).<sup>61,62</sup> Although perioperative management of patients who are receiving antiplatelet therapy is a common clinical occurrence, there are minimal high-quality studies to direct, continue or interrupt antiplatelet therapy, as well as concerning the role of bridging therapy.<sup>63</sup>

## MANAGEMENT

Management strategies for IBDs must consider both episodic and preventive approaches for patient care. Compared to the general population, patients with IBDs are at 1.5 and 5 times greater risk for hemorrhage and transfusion, respectively.<sup>64–67</sup> Short-term prophylaxis is warranted mainly to provide effective hemostatic coverage to patients undergoing surgery or invasive procedures, at the time of labour and delivery, or with recurrent excessive menstrual bleeding. Long-term prophylaxis is used to prevent bleeding in patients at increased risk for frequent and spontaneous bleeding in the joints, nose or gastrointestinal tract (Table 3).<sup>2,59</sup>

### Menorrhagia

The initial clinical presentation of an IBD in female adolescents and adults is commonly associated with menorrhagia. The primary management pathway and drug or replacement products that may be required before diagnosis of an IBD etiology are summarized in Figure 2<sup>34</sup> and Table 3.<sup>2,59</sup> Educational counselling is required for the informed-consent process. With an IBD diagnosis, discussion of treatment and choice needs to include the patient's

long-term fertility choice, contraception needs, IBD etiology, bleeding severity, and social or religious factors.

Hormonal therapy is indicated for women who want to preserve their fertility options but are not planning an immediate pregnancy (within 12–18 mo). Evidence-based assessment of hormonal therapy in patients with IBDs is limited (Table 5).<sup>68</sup> Additional risk counselling may be required, as some women with IBDs have an increased risk of thromboembolic events (afibrinogenemia), and factor replacement may be required for women with a severe bleeding phenotype if they do not respond to medical therapy.

### von Willebrand disease

Surgical prophylaxis is required for major and minor surgical procedures in patients with vWD.<sup>44</sup> The American Society of Hematology, the International Society on Thrombosis and Haemostasis, the National Hemophilia Foundation and the World Federation of Hemophilia formed a multidisciplinary guideline panel to establish evidence-based guidelines intended to support patients, clinicians and health care professionals in their decisions about management of vWD. Following are their clinical consensus-based recommendations for vWD management.<sup>69</sup>

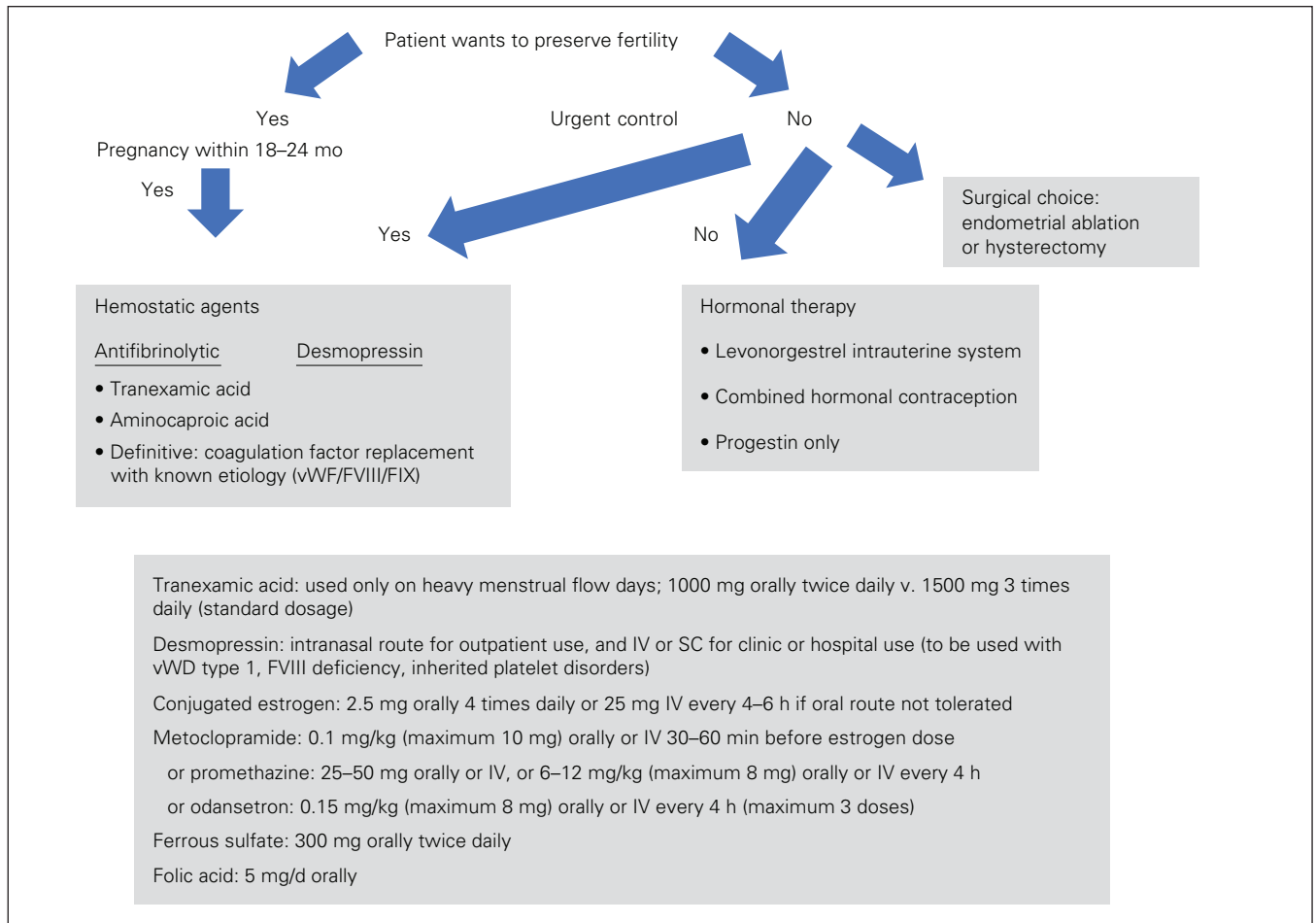
#### Prophylaxis therapy

- Recommendation 1: in patients with vWD with a history of severe and frequent bleeds, the panel suggests the use of long-term prophylaxis rather than no prophylaxis.

*Desmopressin challenge (trial and administration):*

- Recommendation 2A: desmopressin is a valid treatment option for patients with vWD type 1 with a baseline vWF level less than 0.30 IU/mL. The panel suggests a trial of desmopressin and treating with desmopressin





**Fig. 2.** Decision guide for acute heavy menstrual bleeding (defined as any menstrual bleeding that interferes with daily activity [work, housework, leisure or sport, social activity] during most menstrual periods; bleeding is significant for any 1 of these scenarios: changing pads within 2 h, bleeding lasting ≥ 7 d, clot size > 1 cm with “flooding,” pictorial blood assessment chart score > 100).<sup>34</sup> F = factor; IV = intravenously; SC = subcutaneously; vWD = von Willebrand disease; vWF = von Willebrand factor.

| Hormonal product   | Efficacy   | Other clinical factors   |
|--|--|--|
| Levonorgestrel-releasing intrauterine system   | Most effective therapy for heavy menstrual bleeding  | <ul style="list-style-type: none"> <li>• Provides 5 yr of therapy</li> <li>• Contraception failure rate &lt; 0.1%</li> <li>• Removal requested by patient in 17%–20% of cases</li> <li>• Spontaneous expulsion rate 8% (decreased with associated use of tranexamic acid)</li> </ul> |
| Combined hormonal contraception (birth control pill, transdermal patch and vaginal ring) | Effective for contraception and menses suppression   | <ul style="list-style-type: none"> <li>• Can be used monthly or continuously for 12 mo</li> <li>• Break-through bleeding can occur</li> </ul>  |
| Progesterone only (pill, intramuscular medroxyprogesterone or intradermal implant)       | Reduces menstrual blood loss with irregular bleeding | —  |

based on the results over not performing a trial and treating with tranexamic acid or coagulation factor concentrate.

- Recommendation 2B: for these patients, the panel suggests against treating with desmopressin in the absence of desmopressin trial results.

**Antithrombotic therapy (as required)**

- Recommendation 3: in patients with vWD and cardio-

vascular disease who require treatment with antiplatelet agents or anticoagulant therapy, the panel suggests giving the necessary therapy over no treatment.

- Recommendation 6A: the panel suggests using either hormonal therapy (combined hormonal contraception) or levonorgestrel-releasing intrauterine system, or tranexamic acid over desmopressin to treat women with heavy menstrual bleeding who do not wish to conceive.

- Recommendation 6B: the panel suggests using tranexamic acid over desmopressin to treat women with heavy menstrual bleeding who wish to conceive.

### Major surgery

- Recommendation 4A: the panel suggests targeting both FVIII and vWF activity levels of 0.50 IU/mL or greater for at least 3 days after surgery.
- Recommendation 4B: the panel suggests against using only FVIII level of 0.50 IU/mL or greater as a target level for at least 3 days after surgery.

General surgical options are appropriate for women with IBD who do not want to preserve their fertility options. Multidisciplinary counselling should be used for informed consent and choice. Endometrial ablation is a minimally invasive procedure that is appropriate for women with no uterine or pelvic disorders, as it reduces blood loss substantially in women with IBDs. Hysterectomy provides a definitive surgical treatment for women with IBDs and heavy menstrual bleeding, or uterine or pelvic disorders. There is an operative and anesthesia risk, estimated at 1%–3% for hysterectomy. Women with IBDs are at increased risk for perioperative bleeding, subsequent red cell transfusion and potential interventional radiology. This hemorrhagic complication risk is important to consider as part of the informed-choice process (Figure 2).<sup>34</sup>

### Minor surgery (invasive procedures)

- Recommendation 5A: in patients undergoing minor surgery or minor invasive procedures, the panel suggests increasing vWF activity levels to 0.50 IU/mL or greater with desmopressin or factor concentrate with the addition of tranexamic acid over raising vWF levels to 0.50 IU/mL or greater with desmopressin or factor concentrate alone.
- Recommendation 5B: in patients with vWD type 1 with baseline vWF activity levels greater than 0.30 IU/mL and a mild bleeding phenotype who are undergoing minor dental mucosal procedures, the panel suggests giving tranexamic acid alone over increasing vWF activity levels to 0.50 IU/mL or greater with any intervention.

### Other von Willebrand disease bleeding events

In severe trauma or moderate to severe bleeding, if the coagulation factor level is less than 1%–30% or less than 30%–60%, the use of factor replacement dependent on the percent deficiency level can be considered.<sup>41,42</sup>

### X-linked hemophilia A and B carrier status

Many female hemophilia A carriers are at risk for abnormal bleeding, but these carriers are underrecognized by health care providers, and their bleeding symptoms are underreported.<sup>70</sup> Low FVIII levels are consistently associated with clinically significant bleeding and correlate with

female skewed X chromosome inactivation. Bleeding can occur in some hemophilia A carriers with normal FVIII levels.<sup>70</sup> Chaudhury and colleagues<sup>45</sup> reported that females with mild hemophilia (FVIII/FIX) and a bleeding phenotype (traumatic/joint/clinical bleeding) were managed with factor concentrates or antifibrinolytics, but heavy menstrual bleeding was more difficult to control.

Nongynecologic bleeding occurs in female hemophilia carriers owing to the genetic mechanisms described, and their bleeding management may be similar to that for males with hemophilia. Prophylactic management for affected female carriers minimizes bleeding risk and morbidity in joints and the central nervous system (increased with age > 60 yr and hypertension). Prophylactic management should consist of replacement of the appropriate coagulation factor after the diagnosis has been identified and an individualized prophylaxis regimen has been determined based on the patient's peak–trough FVIII levels. An accessible app (WAPPS-hemo) is available to assist in managing the patient's regimen.<sup>54</sup> The prophylactic use of noncoagulation factor therapy (emicizumab) can be considered as more evidence accrues.<sup>52</sup>

### Inherited platelet disorders

Potential curative treatments for inherited platelet disorders include allogenic hematopoietic stem cell transplantation and gene therapy.

Technologic diagnostic improvements have not been translated into clinical management. Therapies to increase platelet count, mitigate platelet dysfunction and definitively correct inherited thrombocytopenia continue to be used.<sup>30,31,55</sup>

### Outpatient management<sup>29,71</sup>

As a first-line option, initial control will be obtained with desmopressin in 40% of cases and with an oral contraceptive pill in 30%.<sup>71</sup> At 2 years, control will be achieved with an oral contraceptive pill or desmopressin in 50% of cases.<sup>71</sup> Additional options for the 50% of cases not controlled by either of these medications include

- Nonhormonal therapy: specific factor replacement, antifibrinolytic agent (tranexamic acid or aminocaproic acid) or desmopressin
- Hormonal therapy: combined estrogen–progestin product or progestin only
- Combination depends on the patient's contraception needs, whether an estrogen product is contraindicated, the patient's ability to tolerate an estrogen product, and major adverse effects or sensitivities (there is no real risk in using an antifibrinolytic with estrogen).

### Directed procedural/surgical management via bleeding risk assessment<sup>31</sup>

- Prevention/prophylaxis of mild to moderate inherited platelet disorder bleeding

- ♦ Topical measure: compression with gelatin sponges for wounds, epistaxis and bleeding after dental surgery
- ♦ Antifibrinolytic drugs: treatment before procedure and for 3–5 days afterward: 1) tranexamic acid, 15–25 mg/kg orally every 8 hours; 2) desmopressin, 150 µg/dose intranasally, 0.3 µg/kg subcutaneously or 0.2–0.3 µg/kg in saline (4 µg/mL) intravenously over 30 minutes starting 1 hour before procedure.
- Prevention of moderate to severe inherited platelet disorder bleeding
  - ♦ Antifibrinolytic drugs: severe bleeding, tranexamic acid, 10 mg/kg intravenously every 8 hours
  - ♦ Platelet transfusion: essential; leukocyte-depleted platelet concentrate is preferable; recommended preprocedure platelet count is greater than 30 × 10<sup>9</sup>/L for dental or minor surgery, greater than

50–80 × 10<sup>9</sup>/L for major surgery or vaginal or cesarean delivery, and greater than 100 × 10<sup>9</sup>/L for eye or central nervous system surgery

- ♦ Recombinant active factor VII: approved for Glanzmann thrombasthenia; off label for Bernard–Soulier syndrome; potentially useful in combination with antifibrinolytics for control of bleeding in childbirth in women with severe platelet dysfunction; 90–120 µg/kg intravenously before the procedure and then every 90–120 minutes until hemostatic control is attained.

**Pregnancy**

Obstetric management for women with vWD, hemophilia carriers and those with inherited platelet disorders requires counselling (preferably before conception), choice, informed

**Table 6. Pregnancy and percutaneous procedure (pregnancy or gynecology) management protocols for patients with inherited bleeding disorders<sup>2,40,59,72–81</sup>**

| Condition                | Primary coagulation issue     | Female bleeding phenotype                                     | Pregnancy: factor change ante partum and/or at delivery*   | Percutaneous procedure†   |                   |   |
|--------------------------|-------------------------------|---|--|---|-------------------|---|
|                          |                               |   |  | Product   | Time before/after | Further dosing; regional anesthesia             |
| von Willebrand disease   |                               |   |  |   |                   |   |
| Type 1                   | vWF level decreased           | Mild to moderate  | Increase vWF-containing concentrates or desmopressin   | vWF-containing factor VIII concentrate  | ≤ 4 h/1–3 d       | • Once per day<br>• Yes if prior > 12 h         |
| Type 2                   | Dysfunctional vWF             | Variable/moderate   | Small increase in vWF-containing concentrates  | vWF-containing factor VIII concentrate  | ≤ 4 h/1–3 d       | • Once per day<br>• Yes if prior > 12 h         |
| Type 3                   | vWF absent                    | Severe  | No increase in vWF-containing concentrates   | vWF-containing factor VIII concentrate  | ≤ 2 h/> 3–5 d     | • Once or twice per day<br>• Yes if prior > 8 h |
| Hemophilia A             | Factor VIII level decreased   | Mild to moderate, with factor VIII level < 40 IU/dL           | • Ante partum: increase factor VIII or desmopressin<br>• Delivery: factor VIII replacement as required | Recombinant factor VIII   | ≤ 2 h/> 3–5 d     | • Once or twice per day<br>• Yes if prior > 8 h |
| Hemophilia B             | Factor IX level decreased     | Mild to moderate, with factor IX level < 40 IU/dL             | • No increase<br>• Delivery: factor XI replacement as required   | Recombinant factor IX   | ≤ 2 h/> 3–5 d     | • Once per day<br>• Yes if prior > 8 h          |
| Glanzmann thrombasthenia | Platelet function disorder    | Associated with severe bleeding phenotype                     | • Avoid blood or platelet transfusion during pregnancy<br>• Delivery: HLA-matched platelets transfused | —   | —                 |   |
| Bernard–Soulier syndrome | Platelet receptor abnormality | Associated with severe bleeding phenotype                     | • Avoid blood or platelet transfusion during pregnancy<br>• Delivery: HLA-matched platelets transfused | —   | —                 |   |
| Factor XI deficiency     | Factor XI level decreased     | Highly variable but increased with factor XI level < 15 IU/dL | • No increase<br>• Delivery: factor XI replacement   | • Factor XI concentrate (plasma-derived)<br>• Fresh frozen plasma in emergency or if no factor XI concentrate | ≤ 8 h/1–3 d       | • Once per day<br>• Yes if prior > 12 h         |

HLA = human leukocyte antigen; vWF = von Willebrand factor.

\*If factor level is less than 40 IU/dL.

†Pregnancy-related (prenatal diagnosis, regional anesthesia), gynecologic or pelvic endoscopy.

**Table 7. Obstetric management for hemophilia carriers**<sup>2,40,59,72–81</sup>

| Item                                      | Hemophilia A  | Hemophilia B  |
|---|---|---|
| Factor levels                             | <ul style="list-style-type: none"> <li>FVIII level increased 2- to 3-fold during pregnancy</li> <li>Median FVIII/FIX levels are 55–68 IU/dL but may range from &lt; 10 IU/dL to &gt; 100 IU/dL</li> </ul>   | <ul style="list-style-type: none"> <li>FIX level increased only slightly</li> <li>As for hemophilia A</li> </ul>  |
| Obstetric clinical area                   |   |   |
| Second- and third-trimester activity      | Multidisciplinary consultations and labour and delivery planning are required   | As for hemophilia A   |
| Second stage before delivery              | Tranexamic acid, 1000 mg orally   |   |
| Anesthesia                                | <ul style="list-style-type: none"> <li>FVIII level &gt; 0.5 IU/dL is required</li> <li>Regional anesthesia risk with coagulation factor levels &lt; 0.5 IU/dL, as prevalence of neuraxial hematoma is 2% with factor levels 1% of normal<sup>76</sup></li> </ul>  | <ul style="list-style-type: none"> <li>FIX level &gt; 0.5 IU/dL is required</li> <li>As for hemophilia A</li> </ul>   |
| Low level of coagulation factor (VIII/IX) | FVIII level < 0.8 IU/dL: FVIII coagulation factor replacement to achieve > 100–150 IU/dL at delivery, or desmopressin, 0.3 µg/kg (prepregnancy weight) nasally or subcutaneously after cord clamping*   | <ul style="list-style-type: none"> <li>FIX level &lt; 1%–30% of normal: FIX coagulation factor replacement at 80 U/kg</li> <li>FIX level &gt; 30%–60% of normal: FIX coagulation factor replacement at 50 U/kg</li> </ul>                                   |
| Delivery                                  | <ul style="list-style-type: none"> <li>Use of ventouse, midcavity forceps, fetal scalp blood sampling, fetal scalp electrode should be avoided in fetuses at risk</li> <li>Active third-stage management with evaluation of vaginal blood loss</li> </ul>   | <ul style="list-style-type: none"> <li>As for hemophilia A</li> <li>As for hemophilia A</li> </ul>  |
| Postpartum hemorrhage                     | Prophylaxis therapy: coagulation factor replacement is most common therapy; desmopressin, plasma or tranexamic acid rarely used   | <ul style="list-style-type: none"> <li>FIX level &lt; 1%–30% of normal: tranexamic acid, FIX coagulation factor replacement at 50 U/kg</li> <li>FIX level &gt; 30%–60% of normal: tranexamic acid, FIX coagulation factor replacement at 15 U/kg</li> </ul> |
| Postpartum period                         | <ul style="list-style-type: none"> <li>Maintain FVIII level &gt; 0.5 IU/dL for 3 d with vaginal delivery and 5 d with cesarean delivery</li> <li>Tranexamic acid, 1000 mg 3–4 times per day for 7 d, including until lochia is minimal</li> <li>Hospital- and home-based monitoring of blood loss should be reported to obstetric provider</li> </ul> | <ul style="list-style-type: none"> <li>Maintain FIX level &gt; 0.5 IU/dL for 3 d with vaginal delivery and 5 d with cesarean delivery</li> <li>As for hemophilia A</li> <li>As for hemophilia A</li> </ul>  |

FIX = factor IX; FVIII = factor VIII.

\*Desmopressin is safe in the first and second trimesters, but safety at delivery has not been shown (risk of fluid overload and hyponatremia/fluid restriction). Saline use and sodium evaluation are required.

**Table 8. Preconception or intrapartum counselling and informed consent for female hemophilia A and B carriers**

| Study                                     | Summary  |
|---|--|
| Hermans et al., <sup>42</sup> 2018        | Description of the evolution of practice, and unmet needs and options for girls and women in families with hemophilia, as well as the clinical and laboratory characteristics during pregnancy.  |
| Hermans et al., <sup>82</sup> 2022        | Choosing the optimal treatment using an integrated, patient-oriented approach to shared decision-making between patients and clinicians.   |
| Mannucci, <sup>83</sup> 2020              | Despite the major advances in prophylaxis obtained with extended half-life factor products and nonfactor therapies, break-through bleeding has not been fully eliminated, and treatment is still physically and psychologically invasive, even when the subcutaneous route of administration is used.  |
| Delgado-Flores et al., <sup>84</sup> 2022 | Results suggest that prophylactic treatment (at low, intermediate or high dosages) is superior to episodic treatment for bleeding prevention. For patients with hemophilia A, bleeding rates seem to have a dose–response effect.  |
| Ellsworth et al., <sup>85</sup> 2021      | Review of background, rationale and potential of nonfactor therapies, as well as pitfalls and expected limitations. Discussion of factor mimetic therapy (emicizumab), siRNA therapeutics, tissue factor pathway inhibitors and serine protease targets.   |
| Kenet et al., <sup>86</sup> 2021          | Despite high adherence to prophylaxis, the continued occurrence of spontaneous and joint bleeding events requiring treatment, and impaired physical functioning was evident in this study. These results illustrate real-world shortcomings associated with regular FVIII prophylaxis for a cohort of patients with severe hemophilia A, for whom additional hemostatic options were needed.   |
| Witarto et al., <sup>87</sup> 2022        | This analysis indicates that ruriotocog alfa pegol could serve as a safe and effective alternative for bleeding prophylaxis in previously treated patients with hemophilia A; however, there are limited direct comparison studies. Moreover, this therapy appears to have low immunogenicity, which further increases the safety profile of the drug in such clinical conditions.   |
| George, <sup>88</sup> 2021                | Current clinical hemophilia gene therapy efforts are focused largely on the use of systemically administered recombinant adeno-associated viral (rAAV) vectors for FVIII or FIX gene addition.   |
| Arruda et al., <sup>89</sup> 2021         | Gene therapy for hemophilia A and B has benefited from advancements in the field of general gene therapy, such as the development of adeno-associated viral vectors and disease-specific breakthroughs, such as the identification of B-domain deleted FVIII and hyperactive FIX Padua. It has also benefited from hemophilia B clinical studies that revealed critical safety concerns related to immune responses to the vector capsid not anticipated in preclinical models.  |
| Gualtierotti et al., <sup>90</sup> 2022   | The management of pain in patients with hemophilia requires more standardization. Pain management is based on analgesics such as paracetamol, the first-line treatment of acute and chronic pain in adults and children, in association with opioids in adults. Since NSAIDs inhibit platelet function, short courses of these drugs are required. Local treatment with intra-articular injections of corticosteroids is an option for refractory cases. Physiotherapy has a role after hemarthrosis and for long-term management of chronic pain for both pediatric and adult patients. |

FIX = factor IX; FVIII = factor VIII; NSAID = nonsteroidal anti-inflammatory drug; siRNA = small interfering RNA.

consent and multidisciplinary care providers (Table 3,<sup>2,59</sup> Table 6,<sup>2,40,59,72–81</sup> Table 7,<sup>2,40,59,72–81</sup> Table 8<sup>42,82–90</sup>). There are substantial hemostatic changes in a normal pregnancy whose role is to preserve placental function and prevent excessive bleeding at delivery.<sup>63</sup>

An individualized protocol for the management of labour and delivery care in women with IBDs is required based on the identified individualized maternal and fetal risk (Table 3, Tables 6–8). Factor VIII levels are not a good predictor of bleeding risk in hemophilia A carriers, as there are no significant differences in FVIII levels for heterozygous carriers of mutations classified as mild, moderate and severe for hemophilia A.<sup>77,78</sup>

Prenatal diagnosis techniques may be required for fetal assessment in women with IBDs after routine serum-based aneuploidy screening. No evidence-based series to determine invasive procedure risks for pregnant people with IBDs were identified. Prenatal diagnosis procedures have been used for maternal management decisions in 50% of female hemophilia carriers.<sup>72,91</sup> In patients with vWD, early genetic testing of the fetus is not routinely recommended owing to gene size and molecular testing, as well as the lack of clinical implication (other than for delivery and neonatal risk), except for couples with a child with autosomal recessive vWD type 3.<sup>72</sup> These couples should have preconception or early pregnancy counselling regarding prenatal testing. Pregnant people with severe autosomal dominant vWD have a 50% chance of having an affected child. For patients with vWD type 1–3, amniocentesis testing at 30–32 weeks can be considered to identify significant fetal risk for labour and delivery management.<sup>72</sup>

Preconception counselling of female hemophilia carriers (obligate or highly possible) is recommended, if possible, to identify the causative mutation, measure FVIII and FIX levels, provide information for the management of pregnancy and delivery, and discuss the pregnant person's options and choice in the case of an affected male fetus. Prenatal diagnosis techniques (chorionic villus sampling, amniocentesis, plasma cell-free placental DNA screening [noninvasive prenatal screening]) and the availability of assisted reproductive technology are options to inform hemophilia carriers' reproductive choice.<sup>92</sup> Plasma cell-free placental DNA screening for a Y chromosome via Y-specific polymerase chain reaction is an early prenatal screening option. If a male fetus is identified, chorionic villus sampling to test for the hemophilia mutation can be done. This procedure is normally done at 10–14 weeks' gestation, via transcervical or transabdominal techniques under ultrasonography guidance. Vaginal bleeding or fetal loss may occur (rate 0.5%–3%). Placental tissue has a 1%–2% biologic risk of confined placental mosaicism.

Second-trimester screening with ultrasonography will identify the gender of the fetus; if male, amniocentesis under ultrasonography guidance to test for the hemophilia mutation can be done.<sup>12,60,72</sup> This procedure is normally

performed at 15–18 weeks but can be done into the third trimester. Amniotic fluid, with amniocyte cells, is used for testing. Procedural risks include minimal bleeding risk, fetal loss (< 1%) and premature rupture of membranes (2%–3%). Direct studies are carried out with the focus on identifying the responsible mutation (intron 22 inversion) in the carrier's *FVIII* gene through full sequencing of the gene. The intron 22 inversion mutation of *FVIII* accounts for 45% of mutations associated with severe hemophilia, and large deletions and duplications are present in 6% of cases; complex rearrangements involving both inversion and deletion/duplication and mosaicism for Inv22 are rare. If the hemophilia mutation testing is not predicted to be severe, the *FVIII* gene can be sequenced directly. Indirect studies are important if the carrier's gene testing does not detect a mutation. The *FVIII* gene is examined for normal variants or polymorphisms within the family to identify which X chromosome is associated with the family hemophilia. Indirect studies always complement direct studies.

In noninvasive prenatal screening, placental cell-free DNA present in the maternal plasma is used for fetal testing (Y chromosome sex; X chromosome analysis). If assisted reproductive technology is used, preimplantation genetic diagnosis can be performed (blastomere or trophoctoderm biopsy, with fluorescence in situ hybridization, polymerase chain reaction or next-generation sequencing).<sup>92</sup> Pregnancy outcomes are facility specific, but generic results indicate delivery in 18% of oocyte retrieval procedures and 25% per embryo transfer procedure.<sup>93</sup>

Directed prelabour anesthesia consultations are recommended for management of regional anesthesia block in labour, with individualized risk assessment and planning. Treatment options of desmopressin acetate or recombinant vWF/FVIII Haemate P (intermediate-purity vWF/FVIII concentrate) (CSL Behring) should normalize coagulation factors and decrease maternal bleeding risk in patients with vWD.<sup>94–99</sup>

Regarding neuraxial anesthesia, the panel recommends the following:<sup>69</sup>

- Recommendation 7: in women with vWD for whom neuraxial anesthesia during labour is deemed suitable, the panel suggests targeting a vWF activity level of 0.50–1.50 IU/mL over targeting an activity level of more than 1.50 IU/mL to allow neuraxial anesthesia.

Directed obstetrical delivery management for fetal vWD type 1–3 and hemophilia A and B risk (using a stratification process for estimated obstetric bleeding risk levels of mild, moderate and high [Table 3, Tables 6–8]) suggests that, in pregnant people with associated mild or unlikely risk, a recommendation for avoidance of ventouse use and external cephalic version, and selected use of rotational forceps, fetal scalp blood sampling and fetal scalp electrodes should be considered.<sup>2,40,59,72–81</sup> In those with associated moderate risk, care providers should consider a recommendation for avoidance of use of midcavity or rotational forceps,

ventouse use procedure and external cephalic version, and selected use of fetal scalp blood sampling and fetal scalp electrodes. In those with associated high risk, a recommendation for avoidance of use of all forceps, external cephalic version, ventouse procedure, fetal scalp blood sampling and fetal scalp electrodes should be considered.

Regarding the postpartum period, the panel recommends the following:<sup>69</sup>

- Recommendation 8: the panel suggests the use of tranexamic acid over not using tranexamic acid in women with vWD type 1 or low vWF levels (which may apply to vWD type 2 and 3) during the postpartum period.

Neonatal management has identified that the vWF level is raised at birth, but neonates with severe vWD type 1 and vWD types 2 and 3 have continued low vWF and are at risk for bleeding complications.<sup>72</sup> Prenatal risk assessment with amniocentesis at 30–32 weeks can be considered for optimal neonatal planning.<sup>72</sup> Cord blood testing for FVIII and vWF antigen and activity is recommended. Cranial imaging and short-term prophylaxis with factor concentrate should be considered neonates with vWD type 3, especially with a history of traumatic delivery. Oral vitamin K administration is recommended for neonates with vWD type 2 or 3. The smallest-gauge needles should be used for later newborn vaccination dosing. The risks and issues for the neonate and during the first year of life should be reviewed with the parents before discharge.<sup>2,59,72</sup>

Female hemophilia B carriers do not exhibit the hemostatic acute phase reactant elevations with FVIII, and this carrier state may be associated with increased risk of postpartum hemorrhage.<sup>25</sup> Postpartum hemorrhage rates have been found to be higher for carriers with a severe hemophilia mutation (54%) compared to those with a mild mutation (29%).<sup>78–81</sup>

### Best-practice considerations

Best-practice considerations for screening, diagnosis and management of IBDs in female adolescents and adults are presented in Table 9.

### New management considerations

With the management goal of treating the primary deficiency in vWD — vWF — the novel approach of replacing only vWF was introduced about a decade ago. After the manufacture of a concentrate fractionated from human plasma and another obtained through recombinant DNA technology, clinical trials showed that vWF products correct not only the primary vWF deficiency, but also the secondary FVIII coagulant activity deficiency safely and effectively in surgical cohorts.<sup>100</sup> Other clinical areas, such as pediatrics, long-term prophylaxis and recurrent gastrointestinal bleeding due to angiodysplasia, have not been as well researched.

There have been major advancements in management and treatment options for X-linked hemophilia, with prolonged half-life FVIII and FIX concentrates, nonfactor therapies (emicizumab, anti-tissue factor pathway inhibitor antibodies, siRNA targeting of antithrombin) and gene therapy. Fassel and McGuinn<sup>101</sup> reported that these new molecules significantly reduced the burden of hemophilia and improved the quality of life for patients with severe disease. Prophylaxis with FVIII replacement remains the standard of care for male hemophilia A, as nonreplacement products such as prophylactic emicizumab, given subcutaneously every 4 weeks, are not suitable for acute bleeding episodes or management in major surgery.<sup>80,81,102</sup>

Additional treatments to increase platelet count stability, transiently before surgery or via invasive interventions, are<sup>57</sup>

- Splenectomy: for use in Wiskott–Aldrich syndrome or X-linked thrombocytopenia only; may reduce bleeding but increase immunodeficiency and rate of severe infections
- Eltrombopag/romiplostim: recommended for use in Wiskott–Aldrich syndrome, *MYH9*-related disease and thrombocytopenia related to the ankyrin repeat domain 26 gene only.

### Limitations

Limitations of this scoping review are the quality and quantity of the subject-based publications sorted for review, as the selection and elimination of the publications were done by a single author.

### CONCLUSION

Health care providers need to increase their recognition of and support for female adolescents and adults with IBDs. Improved access to counselling, screening, testing and hemostatic management is also required. Patients should be educated and encouraged to report abnormal bleeding symptoms to their health care provider when they have a concern. It is hoped that this review of preoperative IBD diagnosis and management will enhance access to women-centred care to increase patients' understanding of IBDs and decrease their risk of IBD-related morbidity and mortality.

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**Table 9. Best-practice considerations for screening, diagnosis and management of inherited bleeding disorders in female adolescents and adults**

| Consideration no. | Consideration  | Quality of evidence/ strength of recommendation* |
|-------------------|--|--|
| <b>General</b>    |  |  |
| 1                 | IBDs should be considered in the differential diagnosis of all female adolescents and adults presenting with menorrhagia.  | High/strong                                      |
| 2                 | The understanding and recognition of the increased morbidity and low health-related quality of life among female adolescents and adults with menorrhagia, regardless of the etiology, is important for improving patient-oriented health outcomes.   | High/strong                                      |
| 3                 | Adolescents and adults with IBDs should have timely access to regional–provincial hematologic, genetic, obstetric, gynecologic and pediatric multidisciplinary services for screening, diagnosis, education, care and continuing health care support.  | High/weak  |
| <b>Screening</b>  |  |  |
| 4                 | Primary care or gynecologic care providers: a chart defining the minimum criteria for significant bleeding, a history-related bleeding severity scoring tool (ISTH-BAT [International Society on Thrombosis and Haemostasis – Bleeding Assessment Tool]) and a validated graphical scoring system tool (pictorial bleeding assessment chart) are simple and practical methods that can be used by patients to quantify their blood loss.   | High/strong                                      |
| 5                 | Primary care provider should review in detail a list of the patient’s prescription and nonprescription (including over-the-counter and naturopathic products) medications to identify possible medications and products that increase the risk of bleeding.  | Low/weak   |
| 6                 | Primary care providers with adolescent or adult patients presenting with menorrhagia or with positive results from the validated screening assessment tools, or both, should consider obtaining a laboratory bleeding assessment panel (complete blood count, platelet count, ferritin level, fibrinogen level, prothrombin time test and International Normalized Ratio), activated partial thromboplastin time and vWD investigations (factor VIII level, vWF antigen level and functional assay). If a low platelet count is present, further platelet testing (functional and aggregation) should be considered. Thyroid screening can be included if screening testing gives normal results.  | Moderate/strong                                  |
| 7                 | Primary care or pediatric care providers: female adolescents in families with a history of vWD or other IBDs should be tested before the onset of menses to determine whether they have inherited the disease, to allow both the patient and her family to prepare for her first and subsequent menstrual periods.   | Moderate/strong                                  |
| 8                 | Primary care or pediatric care providers: when possible, investigations should be done before oral contraceptive therapy is instituted, as the hormonally induced increase in factor VIII and vWF levels may mask the diagnosis.   | Moderate/strong                                  |
| <b>Diagnosis</b>  |  |  |
| 9                 | Adolescents and adults with a confirmed diagnosis of vWD should be described based on the quantitative (type 1 autosomal dominant, type 3 autosomal recessive) or qualitative (type 2, 2A, 2B, 2M, 2N) evidenced-based subtype.  | Moderate/strong                                  |
| 10                | Adolescents and adults with a confirmed diagnosis of a hemophilia A or B phenotype should be described (and re-evaluated as required) based on the clinical risk category criteria (mild, moderate, severe, symptomatic carrier, asymptomatic carrier).  | Moderate/strong                                  |
| 11                | Adolescents and adults with a confirmed diagnosis of a hemophilia A or B phenotype should be described based on their genetic inheritance mechanism (homozygosity, compound heterozygosity, hemizyosity, heterozygosity, other).   | Moderate/strong                                  |
| 12                | Adolescent and adults with an inherited platelet disorder should be described based on the specific platelet etiology, given the very low prevalence, the association with people from a consanguineous union, and the variable quantitative and qualitative pathology.  | Moderate/strong                                  |
| <b>Management</b> |  |  |
| 13                | Treatment of menorrhagia in adolescents and adults with IBDs should be individualized according to the defined inherited etiology.   | Moderate/weak                                    |
| 14                | Primary care providers or gynecologic care providers: an IBD is not a contraindication to hormonal therapy (oral contraceptives [II-IB], depot medroxyprogesterone acetate [II-3B], danazol [II-2B], gonadotrophin-releasing hormone analogues [II-3B]), or local treatments (levonorgestrel-releasing intrauterine system [II-IB]) and nonhormonal therapy (tranexamic acid [II IB]), as well as desmopressin (II-IB). These therapies represent first-line treatment.<br>Blood products should not be used for patients with mild bleeding disorders (III-A).  | High/strong<br>High/strong                       |
| 15                | In women with IBDs who no longer want to preserve their fertility, conservative surgical therapy (ablation) and hysterectomy may be options.   | High/strong                                      |
| 16                | To minimize the risk of intraoperative and postoperative hemorrhage, coagulation factors should be corrected preoperatively and monitored postoperatively.   | Moderate/strong                                  |
| 17                | Pregnancy care providers for women with IBDs should adopt a multidisciplinary consultation and care approach, including primary care, obstetrics, maternal–fetal medicine, internal medicine, anesthesia and neonatology. A copy of the multidisciplinary planning recommendations should be given to the patient, and she should be instructed to present it to the health care provider admitting her to the birthing location, as well as ensuring a directed copy is provided to the birthing location.<br>Women with severe bleeding disorders or with a fetus at risk for a severe bleeding disorder should give birth in a hospital (level 3) or where there is access to consultants in obstetrics, anesthesiology, hematology and pediatrics. | High/strong                                      |
| 18                | Pregnancy care providers: owing to the varied etiologies of IBDs, the third-trimester and intrapartum prophylactic or treatment use of coagulation factor replacement, use of tranexamic acid or desmopressin, and platelet transfusion must be clearly agreed on and documented by the team in the second trimester; it may be altered later owing to clinical changes in the pregnancy.  | Moderate/weak                                    |
| 19                | Pregnancy care providers: vacuum extraction, use of forceps and fetal scalp electrodes, and fetal scalp blood sampling should be avoided if the fetus is known or thought to be at risk for a congenital bleeding disorder. Cesarean delivery should be performed for obstetric indications only.  | High/strong                                      |
| 20                | Pregnancy anesthesia providers: epidural anesthesia and spinal anesthesia are contraindicated if there is a coagulation defect. There is no contraindication to regional anesthesia if coagulation is normalized. The decision to use regional anesthesia should be made on an individual basis.   | High/strong                                      |
| 21                | Pregnancy: the risk of early and late postpartum hemorrhage is increased in women with bleeding disorders. Women with IBDs should be advised about the possibility of excessive postpartum bleeding and instructed to report this to their care provider immediately.  | Moderate/strong                                  |
| 22                | Neonatology: intramuscular injections, surgery and circumcision should be avoided in neonates at risk for a severe IBD until adequate investigation and preparation are possible.  | High/strong                                      |

IBD = inherited bleeding disorder; vWD = von Willebrand disease; vWF = von Willebrand factor.  
\*GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system.

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