

# Gynaecological and Obstetric Management of Women With Inherited Bleeding Disorders

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## Abstract

**Objective:** The prevalence of bleeding disorders, notably von Willebrand disease (vWD), among adult women with objectively documented menorrhagia is consistently reported to be 10% to 20% and is even higher in adolescents presenting with menorrhagia.

This consensus document has been developed by a multidisciplinary committee consisting of an anesthesiologist, 2 hematologists, and an obstetrician/gynaecologist and has been endorsed by their relevant specialty bodies. It has been prepared with the express purpose of providing guidelines for both women

with inherited bleeding disorders and for their caregivers regarding the gynaecological and obstetric management of these women, including appropriate anesthesia support where indicated.

**Options:** Diagnostic tools and specific medical and, where appropriate, surgical alternatives to management are reviewed and evidence-based recommendations presented.

**Evidence:** A MEDLINE search of the English literature between January 1975 and November 2003 was performed using the following key words: menorrhagia, uterine bleeding, pregnancy, von Willebrand, congenital bleeding disorder, desmopressin/DDAVP, tranexamic acid, oral contraceptives, medroxyprogesterone, therapy, hysterectomy, anesthesia, epidural, spinal. Recommendations from other society guidelines were reviewed.

## Recommendations

1. Inherited bleeding disorders should be considered in the differential diagnosis of all patients presenting with menorrhagia (II-2B). The graphical scoring system presented is a validated tool which offers a simple yet practical method that can be used by patients to quantify their blood loss (II-2B).
2. Because underlying bleeding disorders are frequent in women with menorrhagia, physicians should consider performing a hemoglobin/hematocrit, platelet count, ferritin, PT (INR) and APTT in women with menorrhagia. In women who have a personal history of other bleeding or a family history of bleeding, further investigation should be considered, including a vWD workup (factor VIII, vWF antigen, and vWF functional assay) (II-2B).
3. Treatment of menorrhagia in women with inherited bleeding disorders should be individualized (III-B).
4. An inherited bleeding disorder is not a contraindication to hormonal therapy (oral contraceptives [II-1B], depot medroxyprogesterone acetate (DMPA) [II-3B], danazol [II-2B], GnRH analogs [II-3B]) or local treatments (levonorgestrel-releasing IUS [II-1B]) and non-hormonal therapy (antifibrinolytic drug tranexamic acid [II-1B]) as well as desmopressin (II-1B). These therapies represent first line treatment. Blood products should not be used for women with mild bleeding disorders (III-A).
5. In women who no longer want to preserve their fertility, conservative surgical therapy (ablation) and hysterectomy may be options (III-B). Clinicians may consult the "SOGC Clinical Practice Guideline: Guidelines for the Management of Abnormal Uterine Bleeding" for an in-depth discussion of the available therapeutic modalities, both medical and surgical. To minimize the risk of intraoperative and post-operative hemorrhage, coagulation factors should be corrected preoperatively with post-operative monitoring (II-1B).

**Key Words:** Menorrhagia, coagulation disorder, pregnancy, von Willebrand

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6. Girls growing up in families with a history of vWD or other inherited bleeding disorders should be tested premenarchally to determine whether or not they have inherited the disease to allow both the patient and her family to prepare for her first and subsequent menstrual periods (III-C).
7. In adolescents presenting with menorrhagia, an inherited bleeding disorder should be excluded (III-B). When possible, investigation should be undertaken before oral contraceptive therapy is instituted, as the hormonally induced increase in factor VIII and vWF may mask the diagnosis (II-B).
8. Pregnancy in women with inherited bleeding disorders may require a multidisciplinary approach. A copy of their 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 centre. Women with severe bleeding disorders or with a fetus at risk for a severe bleeding disorder should deliver in a hospital (level three) or where there is access to consultants in obstetrics, anesthesiology, hematology, and pediatrics (III-C).
9. Vacuum extraction, forceps, 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. A Caesarean section should be performed for obstetrical indications only (II-2C).
10. Epidural 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 (III-C).
11. The risk of early and late postpartum hemorrhage is increased in women with bleeding disorders. Women with inherited bleeding disorders should be advised about the possibility of excessive postpartum bleeding and instructed to report this immediately (III-B).
12. Intramuscular injections, surgery, and circumcision should be avoided in neonates at risk for a severe hereditary bleeding disorder until adequate workup/preparation are possible (III-B).

The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table 1).<sup>13</sup>

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## **INTRODUCTION**

Inherited bleeding disorders affect both men and women. Symptoms are quite variable, depending on the type and the severity of the disease. For the same disease severity, women are often more symptomatic due to excessive menstrual bleeding and peripartum hemorrhage. von Willebrand disease (vWD) is the most frequent inherited bleeding disorder, followed by mild coagulation factor deficiencies such as factor XI deficiency and mild platelet disorders (Table 2). Although hemophilia A and B affect only males, women are carriers of the disease and may be symptomatic.

Menorrhagia is defined as menstrual bleeding which occurs at regular, normal intervals but is excessive in flow or duration.<sup>1</sup> Several recent studies have estimated the prevalence of menorrhagia in women with inherited bleeding disorders to be between 57% and 93%.<sup>2-5</sup> In comparison, approximately 10% of normal women experience menorrhagia.<sup>6,7</sup>

Another way of quantifying the clinical significance of this problem is to determine the number of women presenting to a physician with menorrhagia who, on laboratory analysis, prove to have a definable bleeding disorder. This figure appears to be between 10% and 20%, with vWD comprising approximately 70% of cases.<sup>6,8,9</sup>

Evidence has accumulated that not only is there an increased prevalence of menorrhagia associated with bleeding disorders, but also that this complication significantly disrupts the quality of life of these women.<sup>10,11</sup> Between 40% and 50% of women experiencing menorrhagia report that they are limited in their activities and that they find working more difficult during their menstrual periods.<sup>12</sup>

The purpose of this document is to summarize the available evidence with regards to both the diagnosis and the obstetric and gynaecological management of women with inherited bleeding disorders. Since vWD is the commonest inherited bleeding disorder, most of the recommendations are derived from reports on patients with mild type 1 vWD.

## **DIAGNOSIS**

### **Menorrhagia**

Women's perceptions of the magnitude of their menstrual flow often are not reliable.<sup>14</sup> In particular, women with a bleeding disorder may underestimate their losses if they compare themselves with other women in their family who also may have a bleeding disorder.<sup>15</sup>

The definition of menorrhagia is the loss of greater than 80 mL of blood per menstrual cycle. The use of a graphical scoring system for menstrual bleeding has resulted in a more practical means of quantifying excessive bleeding (Figure 1).<sup>16</sup> The pictorial blood assessment chart is easy for women to use and has a sensitivity of 86% and specificity of 89%<sup>16</sup> for menorrhagia when compared to measured blood loss. The pictorial blood assessment chart can be sent to women for completion before their first visit to the clinic and then reviewed when they are seen.

### **Initial Evaluation**

#### **Gynaecological Assessment**

Gynaecological causes of abnormal vaginal bleeding (e.g., endometrial polyps, submucosal fibroids, cervicitis, cervical and vaginal lesions, etc.) should be excluded. Menorrhagia (i.e., bleeding that is excessive in flow and duration and that occurs at regular, normal intervals) may be due to local or systemic disorders. A complete personal and family history as well as a physical examination including a careful pelvic/vaginal examination should be done. The clinician is directed to the "SOGC Clinical Practice Guideline: Guidelines for the Management of Abnormal Uterine Bleeding"

**Table 1. Criteria for quality of evidence assessment and classification of recommendations**

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is insufficient evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence not to support the recommendation for a diagnostic test, treatment, or intervention.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence not to support the recommendation for use of a diagnostic test, treatment, or intervention.

\*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.<sup>13</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.<sup>13</sup>

for an in-depth discussion of appropriate gynaecological investigations for abnormal bleeding.<sup>17</sup>

An in-depth coagulation investigation should be considered for the patient with menorrhagia in whom gynaecologic causes have been ruled out. However, a high index of suspicion for a possible bleeding abnormality needs to be maintained in all patients with excessive bleeding, as the prevalence of uterine abnormalities in patients with bleeding disorders, related menorrhagia in whom the gynaecologic abnormality is “unmasked” by the bleeding disorder, is uncertain. Some studies have found gynaecologic pathology in a significant number of patients with vWD.<sup>3</sup>

In adolescence, intrauterine pathology is rare and therefore an unlikely cause of menorrhagia. Thus, a coagulation screen may be appropriate as part of the initial assessment, even in the absence of a pelvic examination.

### Medical Assessment

Initial testing should include a platelet count, hemoglobin/hematocrit, ferritin, prothrombin time (PT), and activated partial thromboplastin time (APTT). In addition, thyroid and hepatic screens and a serum prolactin should be considered.

### Further Investigations

A more in-depth investigation should be considered in the following clinical situations: (1) the menorrhagia is present since menarche, (2) there is evidence of anemia or iron deficiency, (3) there is a personal or family history of bleeding after hemostatic challenge (dental extraction, surgery,

or parturition) or a family history of menorrhagia, (4) there is no local cause for menorrhagia. This investigation may include bleeding time or closure time, blood group, and von Willebrand studies (factor VIII, vWF antigen, and vWF functional assay). These tests can be ordered by the gynaecologist or the family physician or, alternatively, the woman may be referred directly to the hematologist. However, interpretation of abnormal or borderline results usually requires referral to a hematology (or an internal medicine) consultant.

As levels of vWF and factor VIII are affected by a number of factors and, therefore, may fluctuate, it may be necessary to test on more than 1 occasion if there is a positive history but normal vWF levels on initial testing (Table 3).<sup>18</sup>

If there is a positive history in the absence of vWD, further investigation may be indicated for mild factor XI deficiency, platelet dysfunction, and other rare disorders (such as  $\alpha$ 2-antiplasmin or factor XIII deficiency) that are not evaluable by screening tests (Table 2).

It is important to have a precise hematological diagnosis because the diagnosis may affect such clinical situations as the treatment of both gynaecologic and nongynaecologic bleeding, the optimal drugs/therapeutic modalities recommended for the management of severe bleeding, guidelines for patient preparation for surgery including preoperative and postoperative management, and information for family counselling.

### Multidisciplinary Clinics

The ideal management of women with inherited coagulation defects who suffer from menorrhagia is through

**Table 2. Most frequent inherited bleeding disorders**

Disorders	Definition	Coagulation tests
<b>Hemophilia A</b>		
Severe	Factor VIII < 2%	Prolonged APTT, low factor VIII
Mild	Factor VIII 2–25%	Prolonged APTT, low factor VIII
Carrier	Factor VIII approx 50%	APTT usually normal, low factor VIII
<b>Hemophilia B</b>		
Severe	Factor IX < 2%	Prolonged APTT, low factor IX
Mild	Factor IX 2–25%	Prolonged APTT, low factor IX
Carrier	Factor IX approx 50%	APTT usually normal, low factor IX
<b>vWD*</b>		
	Low vWF studies†	Prolonged APTT,‡ prolonged bleeding time or closure time,‡ low factor VIII, low vWF antigen† and functional assay
Factor XI deficiency	Low factor XI	Prolonged APTT, low factor XI
Factor VII deficiency	Low factor VII	Prolonged INR, low factor VII
Factor XIII deficiency	Low factor XIII	Normal APTT and INR, low factor XIII
a2-antiplasmin deficiency	Low α2-antiplasmin	Normal APTT and INR, low α2-antiplasmin
Inherited platelet disorder	Platelet dysfunction	Normal platelet count, prolonged bleeding time or closure time,‡ abnormal specific platelet functional assay

\* For vWD, there is no universal classification of disease severity. Most clinicians would consider a patient as severe if the vWF functional assay and (or) the factor VIII levels are < 10% and mild if they are between 10% and 40%.

† vWF antigen may be normal in certain type of vWD.

‡ May be normal.

multidisciplinary clinics. However, at the present time, very few of those clinics exist and they are all located in tertiary care centres. These clinics include a nurse, a clinical hematologist and a gynaecologist who meet with the patient and liaise with the family physician. The ideal multidisciplinary team would have an even broader representation of expertise, and would include a laboratory hematologist, an obstetrician-gynaecologist, an anesthesiologist, a family physician, a social worker, a pharmacist, a laboratory technician, and a secretary.

**Recommendations**

1. Inherited bleeding disorders should be considered in the differential diagnosis of all patients presenting with menorrhagia (II-2B). The graphical scoring system presented is a validated tool which offers a simple yet practical method that can be used by patients to quantify their blood loss (II-2B).

2. Because underlying bleeding disorders are frequent in women with menorrhagia, physicians should consider performing a hemoglobin/hematocrit, platelet count, ferritin, PT (INR), and APTT in women with menorrhagia. In women who have a personal history of other bleeding or a family history of bleeding, further investigation should be

considered, including a vWD workup (factor VIII, vWF antigen, and vWF functional assay) (II-2B).

**TREATMENT OF MENORRHAGIA IN WOMEN WITH BLEEDING DISORDERS**

There is a growing body of evidence that the quality of life of women with inherited bleeding disorders in general, and of women with vWD in particular, is significantly diminished by both the menorrhagia and the resultant anemia.<sup>10</sup> Many effective strategies are available to treat this problem. In general, treatment progresses from medical to surgical approaches, if medical approaches are unsuccessful. The various options should be presented to the patient.

For an overview or complete discussion of the investigation and management of abnormal uterine bleeding in general, the clinician is again directed to the “SOGC Clinical Practice Guideline: Guidelines for the Management of Abnormal Uterine Bleeding.”<sup>17</sup>

The treatments for abnormal bleeding in women with inherited bleeding disorders may be categorized as either medical or surgical (Table 4).

Many of these treatments have been evaluated specifically in the management of women with bleeding disorders,

**Figure 1. Establishing a diagnosis of menorrhagia**  
(Table inspired by JM Higham et al. *Br J Obstet Gynaecol* 1990;97:734–9)

Days	1	2	3	4	5	6	7	8	9	10
<b>PADS</b>										
Lightly soaked 										
Moderately soaked 										
Heavily soaked 										
<b>TAMPONS</b>										
Lightly soaked 										
Moderately soaked 										
Heavily soaked 										
Menstrual score: _____										

most often in those with mild vWD, which is the commonest of the inherited coagulopathies. Other suggested therapies are based on accumulated general menorrhagia therapy data and are extrapolated to the patients with inherited bleeding disorders. There is considerable variation in practice based on personal preferences, and prospective studies are needed to accurately define the relative place of each therapy. Management needs to be individualized and is best undertaken jointly and in a coordinated fashion by the family physician, the hematologist, and the gynaecologist. It is anticipated that this approach will result in a substantial reduction in hysterectomies and a significant enhancement in the quality of life of affected women.

## Medical Therapies

### A. Hormonal treatments

Hormonal therapy is usually the first line of therapy in women with bleeding disorders who present with menorrhagia. All hormonal therapies are considered safe in women with inherited bleeding disorders.

#### 1. Combined oral contraceptives (COCs)

COCs are an effective and safe therapy for menorrhagia, reducing menstrual blood loss by approximately 50%.<sup>19</sup> Unless specifically contraindicated (e.g., in smokers > 35 years of age), combination oral contraceptives are first-line therapy<sup>20</sup> for management of vWD, and they have a high success rate.<sup>21</sup>

These agents work, at least in part, by increasing the plasma levels of factor VIII and vWF. The combination oral contraceptives are the ideal treatment for menorrhagia in

women with vWD who also require effective contraception and control of dysmenorrhea as well as for those requiring ovulation suppression for management of severe mittelschmerz, also known in the vWD patient as “mid-cycle pain syndrome.”

The monophasic pill taken in a continuous non-stop regimen, which eliminates menses altogether, should be considered particularly in women with anemia and in those who experience a hemodynamic challenge with menses. Break-through bleeding (BTB), if mild, can be ignored. If troublesome, it can be treated either by doubling up on COC pills for 3 to 4 days or by applying a 50 mcg transdermal estrogen patch for the same period of time. If the BTB persists, a 50 mcg COC pill can be tried in place of the lower dose preparation.

#### 2. Progestational Agents

##### 2.1 Depot Medroxyprogesterone Acetate (DMPA)

As in the general population, DMPA given as an intramuscular injection once every 3 months is a useful alternative treatment for menorrhagia in women who want contraceptive protection but in whom COCs are contraindicated. This option may be appropriate in women wishing to preserve their fertility or as a temporizing measure in perimenopausal women. Physicians and their patients choosing this alternative should be made aware of the fact that, while amenorrhea is the anticipated outcome, as many as 1/3 of women experience ongoing spotting or bleeding while on therapy.

In patients with a bleeding disorder, after an intramuscular injection is given, pressure should be applied to the

**Table 3. Reasons for fluctuation of vWF levels**

A. Physiologic reasons
Health status
Menstrual cycle/hormonal fluctuations
B. Modification by coexisting conditions
1. Conditions associated with higher vWF levels
Aging
Acute and chronic inflammation
Diabetes
Malignancy
Pregnancy or oral contraceptive use
Stress, exercise
Hyperthyroidism
2. Conditions associated with reduced vWF levels
Hypothyroidism
Blood type O lower than type non-O

injection site for 15 minutes. In the rare event of a severe vWD or other severe bleeding disorder, intramuscular injections are contraindicated.

*2.2 Levonorgestrel-Releasing Intrauterine System (Mirena IUS)*

More recently, another mode of chronic progestin delivery to the endometrium has become available in the form of an intrauterine system (IUS) Mirena. Mirena releases 20 ug of levonorgestrel per day, which effectively suppresses endometrial growth and significantly reduces menstrual bleeding, clotting, and dysmenorrhea. This device has been extensively evaluated in women with severe menorrhagia awaiting hysterectomy. Use of the Mirena IUS reduced menstrual blood loss by between 74% and 97% and resulted in 64% to 82% of women subsequently cancelling their hysterectomies.<sup>22,23</sup> General acceptance of this device is excellent, but reported side effects, probably arising from the systemic absorption of the norgestrel, include weight gain, headache, depression, acne, prolonged bleeding, and spotting. As the levonorgestrel-releasing IUS has become available only recently, few data are available as to its efficacy, specifically in the management of menorrhagia in women with inherited bleeding disorders, but it is considered safe and an appropriate therapeutic option in this patient population.<sup>24</sup>

**3. Danazol/Cyclomen**

Danazol/cyclomen, another effective treatment for menorrhagia, has been used successfully to control excessive bleeding.<sup>24</sup> This drug is a synthetic steroid with mild androgenic properties and has a profound direct effect on

endometrial tissue. Oligo/amenorrhea can be induced with a dose of 100 to 200 mg per day given over a period of 3 months and then can be maintained using a dose of 100 mg per day; even 100 mg every second day may suffice.

**4. Gonadotrophin-Releasing Hormone Analogs (GnRHa)**

The GnRH-induced hypoestrogenism results in endometrial thinning usually to the point of amenorrhea, but the significant side effects, including bone loss and menopausal symptoms such as hot flashes and vaginal dryness, make this treatment less attractive. Furthermore, in vWD patients, this induced hypoestrogenism theoretically further lowers FVIII and vWF levels, theoretically predisposing to even more bleeding. GnRH may be useful in the treatment of menorrhagia if it is used in conjunction with estrogen and progestin addback therapy.

**B. Non-hormonal treatments**

**1. Antifibrinolytic Agents**

The antifibrinolytic drug tranexamic acid substantially reduces the fibrinolytic capacity of menstrual blood, stabilizing the clot, thereby decreasing menstrual blood loss on the average by approximately 50%.<sup>25</sup> It is effective both in women with<sup>26,27</sup> and without underlying bleeding disorders.<sup>25</sup> A major advantage of this very effective treatment is that it only needs to be taken during the menstrual period itself. The standard adult dose of tranexamic acid is 1 gm po q6h, but limited experience with a single, oral, daily 4 gm dose has proven to be equally effective and well tolerated.<sup>26,27</sup> The only common side effect is mild nausea. Tranexamic acid can also be given intravenously (10 mg/kg q6h).

**2. Desmopressin (DDAVP, Octostim)**

Desmopressin, a synthetic analog of vasopressin, can be dosed intranasally, subcutaneously, or by intravenous infusion. It releases vWF from storage sites within endothelial cells increasing vWF, which in turn results in an increase in plasma levels of factor VIII. It is used to treat patients with mild coagulation disorders, namely mild vWD, mild hemophilia A, and mild platelet function disorders.<sup>28,29</sup>

After a standard 0.3 mcg/kg (maximum 20 mcg) intravenous dose of desmopressin, vWF and factor VIII levels increase by 2- to 6-fold from baseline. Maximum levels of factor VIII and vWF are found between 30 and 60 minutes after intravenous infusion and between 30 and 120 minutes after intranasal administration.<sup>30</sup>

Desmopressin dosed by either the intranasal<sup>31</sup> or subcutaneous<sup>32</sup> route is a practical treatment for menorrhagia arising in patients with mild vWD, in hemophilia A carriers, and in those with mild platelet dysfunction.<sup>33</sup> Desmopressin

may be used to complement the effect of antifibrinolytic therapy. Intranasal desmopressin spray (Octostim Nasal Spray – concentration 1.5 mg/mL) is administered as 1 spray in each nostril resulting in a total dose of 300 mcg. The subcutaneous desmopressin dose (Octostim injection) is 0.3 mcg/kg. Desmopressin administration should begin when menstrual bleeding starts and can be repeated at 12- to 24-hour intervals for the first 2 to 3 days of menstruation. Although tachyphylaxis has been reported with frequent repeat doses of desmopressin, a therapeutic response of approximately 70% of the initial increment is usually achieved.<sup>34</sup>

The side effects of desmopressin are usually mild and transient and include facial flushing, headaches, nausea, menstrual-like cramps, and minor changes in pulse and blood pressure. As a synthetic analogue of vasopressin, desmopressin also has an antidiuretic effect that lasts for approximately 24 hours. Thus, for 24 hours after DDAVP administration, fluid intake should be limited to about 75% of normal to prevent development of significant hyponatremia.<sup>35</sup> Intravenous desmopressin should be administered in the supine position.

### 3. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase and reduce endometrial prostaglandin levels but also interfere with the aggregation of platelets. Thus, in general, in the menorrhagia occurring in patients with vWD and the other inherited bleeding disorders, NSAID use is inappropriate because of the additive effects on excess bleeding. However, the exception may be the COX-2 inhibitors (e.g., Celebrex, Vioxx), which are reported to not cause platelet dysfunction,<sup>36</sup> and may be useful in women with inherited bleeding disorders.

### 4. Iron Deficiency

It is mandatory that women with anemia or iron deficiency secondary to menorrhagia receives adequate iron replacement therapy.

#### C. Blood products

Hormonal and non-hormonal therapies as described above are the mainstay of treatment of women with inherited bleeding disorders, and their use should be considered before resorting to the use of blood products, especially in mild bleeding disorders.

Humate P is the treatment of choice for severe vWD. Humate P is a viral-inactivated, pooled human plasma concentrate containing both factor VIII and vWF. Frozen plasma and cryoprecipitate are not first choice treatment for severe vWD. Their use should be reserved for those emergency situations in which there is an inability to obtain

**Table 4. Treatment options for women with menorrhagia and inherited bleeding disorders**

Medical therapies
A. Hormonal therapies
Combined oral contraceptives
Depot medroxyprogesterone acetate (DMPA)
Levonorgestrel-releasing intrauterine IUS (Mirena)
Danazol/Cyclomen
Gonadotrophin releasing hormone analogs (GnRHa)
B. Non-hormonal Therapies
Antifibrinolytic agents
Desmopressin
NSAIDs (COX-2 inhibitors)
Iron replacement
C. Blood products
Humate-P
Others
Surgical Therapies
A. Conservative
Endometrial ablation procedures
B. Definitive
Hysterectomy

Humate P rapidly. After IV infusion Humate P replaces the vWF for 12 to 24 hours.

Desmopressin has no effect on factor IX. For factor IX deficiency carriers, recombinant F IX is available and would be the first choice of treatment if replacement therapy is required.

Many patients with factor XI deficiency do not experience abnormal bleeding. Thus, if the deficiency is mild and there is no history of significant bleeding, treatment can usually be withheld. When treatment is required, human plasma is generally the treatment of choice. Factor XI concentrate is available but may be associated with thrombosis. There is limited but successful experience with desmopressin in patients with factor XI deficiency.<sup>37</sup>

#### Surgical Therapies

See the “SOGC Clinical Practice Guideline: Guidelines for the Management of Abnormal Uterine Bleeding” for a complete discussion of the surgical alternatives.<sup>17</sup>

#### Conservative Surgery: Endometrial Ablation

In women with inherited bleeding disorders who present with abnormal uterine bleeding, endometrial ablation is a safe and effective treatment option. The use of second-

generation endometrial ablation technologies (global ablation) or hysteroscopic rollerball electrocoagulation might be safer and easier to perform than hysteroscopic resection. Global endometrial ablation using a thermal balloon has been used in women with coagulopathies.<sup>38</sup> Care must be taken to minimize the risk of traumatic complications during cervical dilation by using preoperative cervical softeners and avoiding the use of a tenaculum.

### Definitive Surgical Therapy: Hysterectomy

Hysterectomy is the definitive treatment for menorrhagia in accordance with the “SOGC Clinical Practice Guideline: Guidelines for the Management of Abnormal Uterine Bleeding.” Care must be taken to normalize the coagulation factors preoperatively in order that the risks of intra- and post-operative hemorrhage be minimized.

### Recommendations

3. Treatment of menorrhagia in women with inherited bleeding disorders should be individualized (III-B).

4. An inherited bleeding disorder is not a contraindication to hormonal therapy (oral contraceptives [II-1B], depot medroxyprogesterone acetate [II-3B], danazol [II-2B], GnRH analogs [II-3B]) or local treatments (levonorgestrel-releasing IUS [II-1B]) and non-hormonal therapy (antifibrinolytic drug tranexamic acid [II-1B]) as well as desmopressin (II-1B). These therapies represent first-line treatment. Blood products should not be used for women with mild bleeding disorders (III-A).

5. In women who no longer want to preserve their fertility, conservative surgical therapy (ablation) and hysterectomy may be options (III-B). Clinicians may consult the “SOGC Clinical Practice Guideline: Guidelines for the Management of Abnormal Uterine Bleeding” for an in-depth discussion of the available therapeutic modalities, both medical and surgical. To minimize the risk of intraoperative and post-operative hemorrhage, coagulation factors should be corrected preoperatively with post-operative monitoring (II-1B).

## MANAGEMENT OF THE PERIMENARCHAL ADOLESCENT PATIENT

Premenarchal testing of female members in families with a history of inherited bleeding disorders is recommended. Maintaining a “high index of suspicion” when adolescents present with bleeding problems, such as mucocutaneous bleeding or hemorrhage at menarche, should increase the likelihood of early diagnosis. Premenarchal diagnosis allows us to prepare both the young adolescent and her family to physically and emotionally manage her first period and those that follow.

Continued counselling will help relieve the anxieties that the adolescent may have about her periods in general. Discussion should include a review of the drugs available to regulate her cycles, particularly the anovulatory bleeding pattern of adolescence, and drugs used to control heavy menses, as well as what medications to avoid. The significance of mittelschmerz (the mid-cycle pain associated with ovulation) and its appropriate management, and, of course, contraceptive issues, should be addressed. Parents (as well as the adolescent herself) should be informed about the safety and the appropriateness of the use of COCs, whether prescribed for contraception or for control of bleeding. The patient should be reassured that her future fertility will not be affected but that her children may inherit the disease.

Early introduction to the multidisciplinary team is important. The patient should be encouraged to learn as much as she can about her bleeding disorder. She should be made aware of the many resources and organizations available to her, including sources of excellent information about inherited bleeding disorders and their management.

### Menarche

A significant proportion of adolescents presenting with menorrhagia at menarche have been found to have a bleeding disorder.<sup>20,39</sup> Excessive menstrual bleeding starting at menarche is a particularly frightening problem for adolescent girls and, even more so, for girls with inherited bleeding disorders. This topic should be discussed ahead of time with the young woman and her family. It is important to counsel the patient on how much bleeding is “too much,” on feminine protection products available to her, and about when medical consultation should be sought. She should know that there is a variety of drugs that can manage her abnormal bleeding.

### Recommendations

6. Girls growing up in families with a history of vWD or other inherited bleeding disorders should be tested premenarchally to determine whether or not they have inherited the disease to allow both the patient and her family to prepare for her first and subsequent menstrual periods (III-C).

7. In adolescents presenting with menorrhagia, an inherited bleeding disorder should be excluded (III-B). When possible, investigation should be undertaken before oral contraceptive therapy is instituted, as the hormonally induced increase in factor VIII and vWF may mask the diagnosis (II-B).

## **PREGNANCY IN PATIENTS WITH BLEEDING DISORDERS**

Pregnancy is not contraindicated in patients with coagulation disorders but requires a multidisciplinary approach to management. Ideally, there should be a pre-pregnancy discussion between the future parents and the medical team.

### ***Physiological Response Expected in Pregnancy in Women With Bleeding Disorders***

Factor VIII and vWF antigen and activity usually increase significantly during pregnancy in women with type 1 vWD<sup>40-42</sup> and in hemophilia A carriers. They reach their maximum between 29 and 35 weeks.<sup>40,43</sup> Factor IX and XI levels usually do not change significantly during pregnancy.<sup>42,43</sup> Because factor levels are not predictable during pregnancy, repeat testing during the third trimester is recommended. After delivery, factor levels usually return to baseline levels in 7 to 10 days, but sometimes the drop occurs earlier.<sup>44</sup>

### ***Management of the Pregnancy***

#### ***During pregnancy***

Bleeding due to the coagulation disorder itself is rare during pregnancy. If an invasive diagnostic (e.g., amniocentesis) or therapeutic procedure is planned during pregnancy, factor levels, appropriate for the disorder, should be measured prior to the procedure. A factor level of 0.5 U/mL is generally considered adequate for diagnostic techniques as well as for delivery in women with type 1 vWD.<sup>45</sup> If the mother is a hemophilia carrier, genetic counselling is mandatory. Prenatal diagnosis is outside the scope of this paper. In X-linked diseases, determination of the baby's sex by ultrasound is recommended because the information will be useful to the obstetrician at the time of delivery.

In preparation for delivery, factor levels should be measured during the third trimester (preferably at 32 to 34 weeks). When these third trimester factor level results are available, final recommendations for the delivery should be discussed with the woman and written in the chart along with the underlying rationale for the decision. In addition, a copy of the recommendations should be given to the patient so that she can give it to the team who admits her at the time of delivery. It is important that women with severe bleeding disorders or with a fetus at risk for a severe bleeding disorder deliver in a hospital where there is access to consultants in obstetrics, anesthesiology, hematology, and pediatrics. It is also mandatory to have access to a proper transfusion department with the necessary coagulation factors if needed.

#### ***Labour and delivery***

While it would be ideal to have factor levels done on admission, this is impractical. There should be very little variation between the levels measured during the third trimester and those performed on admission. The factor level considered adequate for vaginal delivery and Caesarean section is 0.5 U/ml in women with type 1 vWD.<sup>45</sup>

An inherited bleeding disorder is not an indication per se for delivery by Caesarean section; a decision to proceed with a Caesarean section should be based on obstetric indications.<sup>46</sup> The delivery should be as atraumatic as possible, minimizing maternal genital tract and (or) perineal lacerations. Vacuum extraction and forceps should not be used, nor should fetal scalp sampling for blood gases be done, nor scalp fetal electrodes used.<sup>46</sup>

#### ***Postpartum***

In the general population, the risk of early postpartum hemorrhage (during the first 24 hours after delivery) is 4% to 5%. This risk is clearly increased to 16% to 22% in patients with vWD, with factor XI deficiency, and for hemophilia carriers.<sup>42,47</sup> The risk of late postpartum hemorrhage is also increased to 11% to 24% in women with bleeding disorders compared to less than 1% in the general population.<sup>41,42,47</sup> It is generally recommended to keep factor levels above 0.5 U/ml for 3 to 4 days after a vaginal delivery and 4 to 5 days after a Caesarean section.<sup>45</sup> Women at risk of late postpartum hemorrhage should have their hemoglobin checked before discharge. They should be instructed about possible excessive bleeding and should be seen in a follow-up visit 2 weeks postpartum.

#### ***Obstetric Anesthesia***

If coagulation is normal in type 1 vWD (as determined by third trimester testing) many anesthesiologists will provide epidural analgesia.<sup>48,49</sup> An advantage of epidural analgesia is that the epidural block can be extended to provide anesthesia should an operative Caesarean delivery be necessary.

Regional analgesia/anesthesia (epidural, spinal) is contraindicated if there is evidence that coagulation is abnormal at the time of administration of neuraxial block, due to the risks of a neuraxial hematoma.<sup>50</sup> Neuraxial hematomas are rare in women with normal coagulation (1:150 000–1:220 000) and are known to be increased in those with a coagulopathy.<sup>50</sup> Because neuraxial hematomas can occur with removal of an epidural catheter, the epidural catheter should be removed when coagulation is normal. In type 1 vWD, this will usually involve removing it immediately postpartum, as vWF levels decrease postpartum. Pudendal blocks are also contraindicated in patients with abnormal coagulation. Intramuscular injections should be avoided in patients with severe inherited bleeding disorders. If an

epidural is contraindicated, analgesia can be achieved using intravenous opioids (such as fentanyl, meperidine) and (or) nitrous oxide. Appropriate monitoring is necessary when intravenous opioids are used.

Regional anesthesia for Caesarean section is contraindicated if there is evidence of a coagulopathy. If the coagulation status is borderline and the woman has a difficult airway, spinal anesthesia may be an option, but the risks and benefits of general anesthesia and spinal anesthesia must be considered and discussed with the woman. If regional analgesia/anesthesia is used, the woman should be observed postpartum to ensure that the block wears off and that neurological function returns to normal. Symptoms of an epidural hematoma may include flaccid paralysis, back pain, and new onset of numbness, weakness, or bowel and bladder dysfunction. If these symptoms occur in women with a bleeding disorder, it is essential to diagnose the problem quickly (MRI, CT) and evacuate the hematoma promptly. The longer the delay, the more likely that permanent neurological disability will occur.

### Neonate

If the baby is at risk of having a severe bleeding disorder, blood samples of cord blood should be taken for the level of the factor that is low in the mother. In some cases, factor levels are not diagnostic at birth, but the result usually gives an indication as to whether the child is affected and provides baseline levels in case an intervention is required. If the factor levels are not informative, they should be repeated at a later time.

Intramuscular injections should be avoided in neonates at risk for a severe hereditary bleeding disorder and surgery or circumcision postponed in neonates at risk for any hereditary bleeding disorder, until adequate workup/preparation is possible. If vitamin K is not given intramuscularly, it should be given orally or subcutaneously with 10 minutes of pressure to the injection site. When oral vitamin K is chosen, repeat doses are necessary.<sup>51</sup> A trans-fontanel ultrasound should be performed soon after birth in babies known to be affected with a severe bleeding disorder. It is unclear whether a newborn with a severe bleeding disorder should remain in hospital under observation for a longer period of time than usual. However, if the baby is discharged early, it is recommended that a physician see him or her for early follow-up. Neonates with a known inherited bleeding disorder should be registered at the hemophilia centre and usual counselling given to the family. The primary care physician must be made aware that a bleeding disorder has been diagnosed.

### Treatment

#### Labour and Delivery

Concerns have been raised<sup>52</sup> that desmopressin causes uterine contraction with premature labour, intrauterine growth retardation, and hyponatremia. There is no large database to confirm the safety of desmopressin in pregnancy. However, an in vitro study looking at transportation of desmopressin across the placenta in humans,<sup>53</sup> as well as a number of published clinical reports, mainly in pregnant patients with diabetes insipidus, do exist supporting its safety when used during pregnancy.<sup>54</sup>

Clinical experience seems to indicate that it is reasonable to use desmopressin immediately before a Caesarean section. Desmopressin can also be administered once the cord is clamped after delivery, if necessary, without concern. For other indications during pregnancy, the decision should be made individually considering the reassuring information about its safety and considering alternatives such as the use of other drugs or blood products. Desmopressin is not contraindicated during lactation.

For patients with severe vWD, or factor IX or XI deficiency, replacement therapy may be necessary for the delivery. Treatment should be discussed in advance, and the appropriate replacement product should be available at the blood bank.

#### Postpartum

Should late postpartum hemorrhage occur, tranexamic acid and oral contraceptives are first-line therapy for its management. To reduce the risk of postpartum hemorrhage, prophylactic oral contraceptives may be started immediately after delivery and continued for 1 month in those women without a contraindication. The risk of thrombosis might be a concern if antifibrinolytic agents are used postpartum, but the risk is probably reasonable in women without other risk factors.

In women with bleeding disorders who first present during pregnancy, it is important to obtain baseline factor levels a few months after delivery and lactation.

### Recommendations

8. Pregnancy in women with inherited bleeding disorders may require a multidisciplinary approach. A copy of their 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 centre. Women with severe bleeding disorders or with a fetus at risk for a severe bleeding disorder should deliver in a hospital (level three) or where there is access to consultants in obstetrics, anesthesiology, hematology, and pediatrics (III-C).

9. Vacuum extraction, forceps, 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. A Caesarean section should be performed for obstetric indications only (II-2C).

10. Epidural 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 (III-C).

11. The risk of early and late postpartum hemorrhage is increased in women with bleeding disorders. Women with inherited bleeding disorders should be advised about the possibility of excessive postpartum bleeding and instructed to report this immediately (III-B).

12. Intramuscular injections, surgery, and circumcision should be avoided in neonates at risk for a severe hereditary bleeding disorder until adequate workup/preparation are possible (III-B).

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