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Von Willebrand Disease in Women

ABSTRACT: Von Willebrand disease, the most common inherited bleeding disorder among American women, is a common cause of heavy menstrual bleeding and other bleeding problems in women and adolescent girls. Von Willebrand disease and other inherited and acquired disorders of coagulation and hemostasis should be considered in the differential diagnosis of all patients being evaluated for heavy menstrual bleeding, regardless of age. There are many treatment options available for patients with von Willebrand disease and heavy menstrual bleeding, including hormonal and nonhormonal therapies. A multidisciplinary approach to management, which involves obstetrician–gynecologists and hematologists, results in optimal treatment outcomes. Many resources exist for patients and health care providers through the National Heart, Lung, and Blood Institute; National Hemophilia Foundation; and the American Society of Hematology.

Von Willebrand disease is the most common inherited bleeding disorder among American women, with a prevalence of 0.6–1.3% (1). The overall prevalence is even greater among women with chronic heavy menstrual bleeding, and ranges from 5% to 24% (2, 3). Among women with heavy menstrual bleeding, von Willebrand disease appears to be more prevalent among Caucasians (15.9%) than African Americans (1.3%) (3, 4).

An autosomally inherited congenital bleeding disorder, von Willebrand disease involves a qualitative or quantitative deficiency of von Willebrand factor (vWF), a protein critical for proper platelet adhesion and protection against coagulant factor degradation. Dominant and recessive patterns of inheritance exist. There are three main types of von Willebrand disease. Type 1 (deficiency of vWF), the most common, is usually mild; type 2 (abnormal vWF) has several subtypes and is less common; and type 3 (absence of vWF), which is rare, is the most severe form (1).

Presenting Symptoms and Signs

Abnormal uterine bleeding is a commonly reported symptom among women with a diagnosis of von Willebrand disease, with 74–92% experiencing heavy menstrual bleeding (5). Additional symptoms or signs that may be present include epistaxis (38–63%), gingi-

val bleeding (26–35%), bleeding after dental extraction (29–52%), bleeding from minor cuts or abrasions (36%), postoperative bleeding (20–28%), gastrointestinal bleeding (14%), and joint bleeding (6–8%) (6, 7).

Evaluation and Diagnosis

Because of the prevalence of von Willebrand disease as well as other inherited and acquired disorders of coagulation and hemostasis in women who seek evaluation for heavy menstrual bleeding, these conditions should be considered in the differential diagnosis of all women who are evaluated for heavy menstrual bleeding, regardless of age (8). Details on the evaluation and management of women who present with abnormal uterine bleeding are addressed in other publications from the American College of Obstetricians and Gynecologists (the College) (8, 9).

The first step in the evaluation of women with suspected bleeding disorders involves obtaining a detailed medical history and performing a physical examination (7, 10). Women with heavy menstrual bleeding since menarche, postpartum or surgical hemorrhage, plus additional bleeding symptoms, such as bruising, epistaxis, gingival bleeding, or family history of bleeding disorder are considered at risk. **Box 1** includes a screening tool to help clinicians identify adult patients who may benefit

Box 1. Clinical Screening for an Underlying Disorder of Hemostasis in the Adult Patient With Excessive Menstrual Bleeding* ↵

Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be structured by the medical history. A positive screening result* comprises the following circumstances:

- Heavy menstrual bleeding since menarche
- One of the following conditions:
 - Postpartum hemorrhage
 - Surgery-related bleeding
 - Bleeding associated with dental work
- Two or more of the following conditions:
 - Epistaxis, one to two times per month
 - Frequent gum bleeding
 - Family history of bleeding symptoms

*Patients with a positive screening result should be considered for further evaluation, including consultation with a hematologist and testing for von Willebrand factor and ristocetin cofactor. Data from Kouides PA, Conard J, Peyvandi F, Lukes A, Kadir R. Hemostasis and menstruation: appropriate investigation for underlying disorders of hemostasis in women with excessive menstrual bleeding. *Fertil Steril* 2005;84:1345–51.

from laboratory testing for disorders of hemostasis. Physical examination findings that may suggest a bleeding disorder include petechiae, ecchymoses, or other evidence of recent bleeding, although absence of these signs does not exclude the possibility of an underlying bleeding condition (7).

In patients with a positive screening history, laboratory testing is indicated (see Fig. 1) (7, 10, 11). An ideal laboratory screening panel to exclude an underlying bleeding disorder is not clearly defined. See Figure 1 for laboratory tests for suspected bleeding disorders. If a patient’s medical history is suggestive of an underlying bleeding condition, specific tests for von Willebrand disease may be indicated, including von Willebrand-ristocetin cofactor activity, vWF antigen, and factor VIII (see Fig. 1) (7, 10, 11). These test results may be affected by several variables, including stress (eg, surgery, anxiety, or exercise), systemic inflammation or anemia, pregnancy, oral contraceptives, time of the menstrual cycle, sample processing, and the quality of the laboratory (7). Repeat testing may be necessary to establish a definitive diagnosis. Obtaining a blood specimen for laboratory testing before administering hormonal treatment may be beneficial in some cases. Because existing laboratory assays have limitations and no single diagnostic test reliably identifies von Willebrand disease, it is recommended that these tests be performed and interpreted in con-

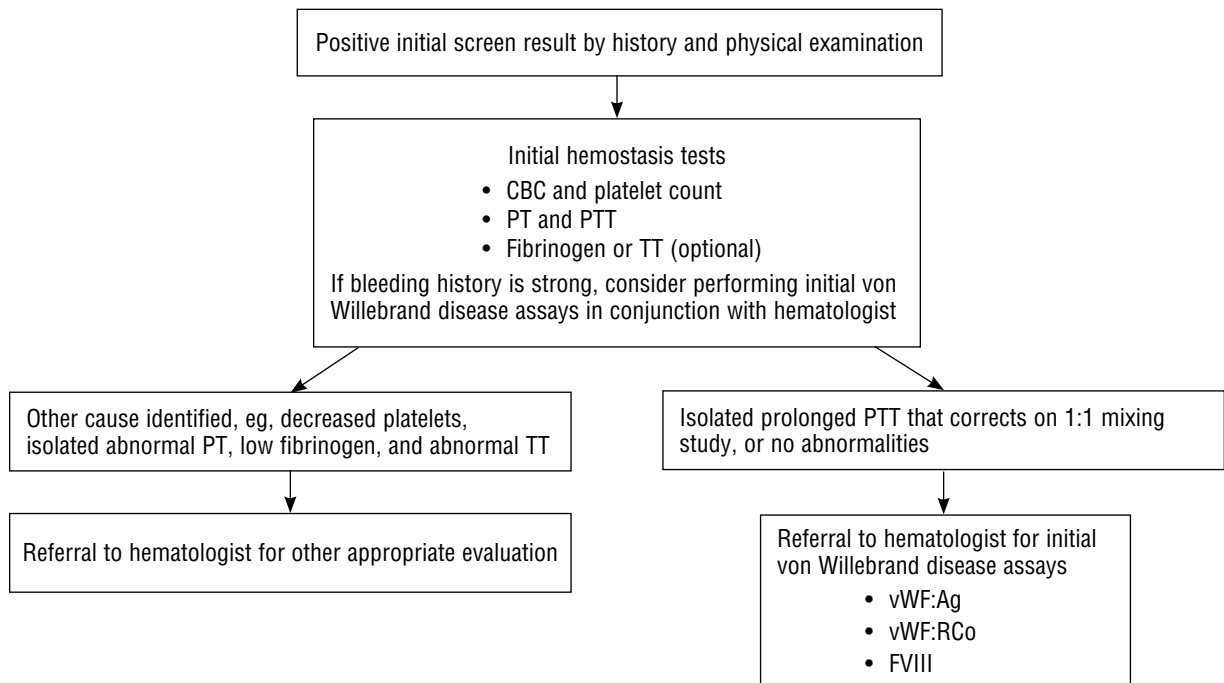


Fig. 1. Laboratory tests for suspected bleeding disorders. Abbreviations: CBC, complete blood count; FVIII, factor VIII activity; PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time; vWF:Ag, von Willebrand factor antigen; vWF:RCo, von Willebrand factor ristocetin cofactor activity. Data from National Heart, Lung, and Blood Institute. The diagnosis, evaluation, and management of von Willebrand disease. NIH Publication No. 08-5832. Bethesda (MD): NHLBI; 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/vwd/vwd.pdf>. Retrieved August 9, 2013. ↵

junction with a hematologist (7, 12). The platelet function analyzer-100 closure time can be a useful adjunct in screening for disorders of platelet aggregation, but it lacks sensitivity and specificity to be used alone as a screening test (13). Furthermore, although certain types of von Willebrand disease may be easily distinguished from other bleeding conditions on the basis of laboratory testing, not all types are as straightforward to diagnose. Genetic tests may be necessary for confirmation of certain von Willebrand disease types (7, 10).

Management

Once a diagnosis of von Willebrand disease has been established, a multidisciplinary approach to management, which involves obstetrician–gynecologists and hematologists, results in optimal treatment outcomes (14). Collaboration with a hematologist is recommended to aid in the planning for gynecologic surgery and obstetric management (see “[Obstetric Considerations](#)” later in this document). Hematologic consultation can guide decisions related to vWF replacement, optimization of hematologic parameters for epidural anesthesia placement, and use of vWF or factor VIII if necessary for the control of bleeding. Preprocedure vWF, vWF activity, and factor VIII levels may be important in determining the need for and timing of infusion treatment preoperatively and postoperatively (7, 15, 16). Patients should be reminded that products that prevent platelet adhesion, such as aspirin or nonsteroidal antiinflammatory drugs, should be avoided once von Willebrand disease is diagnosed (7).

Many treatment options are available for women with von Willebrand disease and heavy menstrual bleeding, including hormonal and nonhormonal therapies. This Committee Opinion addresses long-term management of heavy menstrual bleeding in women with bleeding disorders. Management of acute uterine bleeding in women with bleeding disorders is covered elsewhere (17).

Ensuring families have adequate access to care and encouraging the use of medical alert bracelets are also important. Many resources on bleeding disorders exist for patients and health care providers through the National Heart, Lung, and Blood Institute; National Hemophilia Foundation; and the American Society of Hematology (7, 18).

Hormonal Treatments

Limited studies have been conducted on the treatment of heavy menstrual bleeding specifically for women with von Willebrand disease or other disorders of hemostasis; the following treatments are based on this evidence and expert opinion. Studies in women with von Willebrand disease and heavy menstrual bleeding suggest that the levonorgestrel-releasing intrauterine system may be effective for this population (19). Use of progestin-only contraceptives, such as medroxyprogesterone acetate; progestin-only pills; and the progestin implant, also may

reduce menstrual flow in the setting of bleeding disorders (20, 21).

For women without bleeding disorders, use of combined oral contraceptives or the levonorgestrel-releasing intrauterine system reduce menstrual bleeding (22, 23). Limited studies in women with von Willebrand disease and heavy menstrual bleeding suggest these treatments also may be effective for this population (14, 16, 19, 24). Although oral progestins (taken for 21 days of the cycle) and depot medroxyprogesterone acetate are effective for women with heavy menstrual bleeding without bleeding disorders and may be effective for women with bleeding disorders as well, few studies have focused on their use in this specific population (20, 25, 26).

Nonhormonal Treatments

Nonhormonal treatment options include antifibrinolytic agents, such as tranexamic acid and ϵ -aminocaproic acid (27, 28), and treatments that increase endogenous plasma concentration of vWF, replace vWF, or promote hemostasis without affecting vWF. Antifibrinolytics inhibit the conversion of plasminogen to plasmin, which inhibits fibrinolysis and, thereby, help stabilize clots. Tranexamic acid was approved for the treatment of heavy menstrual bleeding by the U.S. Food and Drug Administration in 2009. Studies in women without bleeding disorders demonstrate that tranexamic acid reduces menstrual bleeding by 30–55% in women with heavy menstrual bleeding (28, 29). Theoretically, tranexamic acid also should work in women with von Willebrand disease because it stabilizes clots that have already formed, and clot formation is an essential step in limiting menstrual bleeding.

Therapies generally prescribed in conjunction with a hematologist once a diagnosis of von Willebrand disease is established include desmopressin acetate, recombinant factor VIII, and vWF complex infusion (7, 10). Desmopressin acetate is a synthetic derivative of the antidiuretic hormone vasopressin and works by stimulating the release of vWF from endothelial cells (7). Recombinant factor VIII and vWF complex infusion are plasma-derived concentrates used to replace factor VIII and vWF, respectively. One study demonstrated that women with bleeding disorders had reduced menstrual flow with the use of either intranasal desmopressin or tranexamic acid (30).

Gynecologic Considerations

The association of von Willebrand disease with other gynecologic problems—including ovarian cysts, endometriosis, and leiomyomas—is uncertain (1). Heavy menstrual bleeding or hemorrhagic ovarian cysts may be managed with combined hormonal contraceptives, which can address both the bleeding and the development of hemorrhagic cysts (12). For the acute presentation of a ruptured ovarian cyst, patients with von Willebrand disease may require surgical intervention for hemostasis.

Obstetric Considerations ↩

Obstetric concerns regarding patients with bleeding disorders include spontaneous abortion, mode of delivery, epidural management, operative delivery techniques, and postpartum hemorrhage. Patients with an underlying bleeding disorder are at a high risk of epidural or spinal hematoma (31). Many experts advocate that women with von Willebrand disease may have a vaginal delivery safely, with cesarean delivery reserved for standard indications (7, 10). Because von Willebrand disease can be transmitted as an autosomal dominant or recessive trait, the fetus can have up to a 50% risk of being affected. Procedures, such as fetal scalp electrode or fetal scalp sampling, are better avoided, and circumcision should be postponed until the newborn's vWD status is determined (2). Operative vaginal deliveries, in which there may be an increased risk of trauma to the newborn, should be avoided because of the potential risk of intracranial hemorrhage (15).

In many women, vWF levels increase in pregnancy and, thus, bleeding risk may be lower than it is when a woman is not pregnant. However, vWF and factor VIII levels are important to assess during pregnancy, including in the third trimester to facilitate planning for delivery and in the event of postpartum hemorrhage (12, 15). Collaboration with a hematologist is recommended to aid in the planning for delivery because of the risk of hemorrhage. Once estrogen levels begin to decrease in the postpartum period, some individuals with bleeding conditions may present with delayed hemorrhage. Notably, a large epidemiologic study reported that the risk of postpartum hemorrhage for women with von Willebrand disease was 50% higher than for women without a bleeding disorder (32).

Adolescent Considerations

The onset of heavy menses at menarche is often the first sign of von Willebrand disease. Among a cohort of 38 women with type 1 von Willebrand disease, retrospective analysis of bleeding symptoms revealed that heavy menstrual bleeding at menarche was the most common initial bleeding symptom, which occurred in 53% of women (33). However, adolescence is a time when bleeding patterns can be highly variable. If the heavy bleeding is attributed solely to immaturity of the hypothalamic-pituitary axis, an underlying bleeding disorder may be overlooked. Adolescents may have both immaturity of the hypothalamic-pituitary axis and heavy menses, further complicating the presentation. Careful screening is necessary to avoid delay in diagnosis. The College recommends that an initial reproductive health visit occur between the ages of 13 years and 15 years, which provides clinicians with an opportunity to inquire about menstrual history and screen for bleeding disorders (8, 34). It is particularly important to diagnose bleeding disorders early in children and adolescents because accidental

trauma is the most common source of morbidity and mortality in this age group (7, 15).

In adult patients, prior bleeding challenges, such as surgery, dental work, or childbirth, are more common. In adolescents, however, there often is no previous challenge to the hemostatic system. The pictorial bleeding assessment is a tool to specifically record the number of pads or tampons used during the menstrual period, how many times there was passage of clots, and the number of flooding accidents. This tool has been validated in adult women and demonstrates greater than 80% sensitivity and specificity for scores greater than 100 (35). Although this tool may be helpful, clinical utility may be limited. Specific questions can help one gain a better understanding of how heavy an adolescent is bleeding, including the following: How many pads or tampons do you use in a day? How frequently do you need to change your pad or tampon? Do you have flooding? Do you miss school because of your period? A simple screening tool, which consists of a set of eight questions that focus on bleeding history, is equally sensitive to the pictorial bleeding assessment (Box 2). The combination of a pictorial bleeding assessment score greater than 185 and at least one question with a positive result on the screening questionnaire increased the sensitivity to 95% for the diagnosis of an underlying bleeding disorder and 91% for von Willebrand disease; the positive predictive value was 71% and 5%, respectively (36). Although several screening questionnaires exist to help identify women with heavy menstrual bleeding who need further hemostatic evaluation, the screening tool in Box 2 may be more appropriate for adolescent patients. If screening results are positive, laboratory evaluation is indicated (see Fig. 1). Screening for disorders of hemostasis before starting hormonal treatment is recommended because treatment may interfere with the results and combined

Box 2. Recommended Screening Tool for Adolescent Patients Who Report Heavy Menstrual Bleeding ↩

If a patient meets one or more of the following criteria, it indicates a positive screen result and warrants further evaluation:

1. Menses greater than 7 days and "flooding" or "gushing" sensation or bleeding through pad or tampon in 2 hours
2. History of anemia
3. Family history of bleeding disorder
4. History of bleeding disorder after hemostatic challenge (ie, tooth extraction, surgery, delivery)

Data from Philipp CS, Faiz A, Dowling NF, Beckman M, Owens S, Ayers C, et al. Development of a screening tool for identifying women with menorrhagia for hemostatic evaluation. *Am J Obstet Gynecol* 2008;198:163.e1–163.e8.

oral contraceptive treatment should be interrupted for accurate von Willebrand disease testing. Although recent studies have suggested that interrupting combined hormonal contraceptive therapy for von Willebrand testing may be unnecessary (37), further research in this area is needed. Given emerging controversy surrounding von Willebrand disease testing, consultation with a hematologist may be helpful for the management of patients already taking combined hormonal contraceptives.

Available treatment options for adolescents are similar to those for other women. In adolescents, fertility preservation is paramount; therefore, medical options should be used rather than surgical procedures. Antifibrinolytic agents, such as tranexamic acid and ε-aminocaproic acid, can be effective nonhormonal treatment options for adolescents; however, their use in individuals younger than 18 years is considered “off-label.” As with the adult patient, a multidisciplinary approach to management, which involves both obstetrician–gynecologists and hematologists, results in optimal treatment outcomes.

Conclusion

Von Willebrand disease is a common cause of heavy menstrual bleeding and other bleeding problems in women and adolescent girls. Obstetrician–gynecologists should include von Willebrand disease and other bleeding disorders in the differential diagnosis when evaluating patients with heavy menstrual bleeding, regardless of age. Once a diagnosis is established, collaboration with a hematologist is recommended for the long-term care of patients with bleeding disorders, such as von Willebrand disease. Many resources exist for patients and health care providers through the National Heart, Lung, and Blood Institute; National Hemophilia Foundation; and the American Society of Hematology.

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