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Von Willebrand Disease in Women

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ABSTRACT: Approximately 3 million women in the United States have inherited bleeding disorders. The prevalence of bleeding disorders is particularly high among women with menorrhagia. Von Willebrand disease is the most common inherited bleeding disorder. Once a diagnosis is made, collaboration with a hematologist is helpful for long-term management. Women with von Willebrand disease may be at increased risk for gynecologic and obstetric complications. Many treatments are available for the control of menorrhagia in women with von Willebrand disease, but the first-line therapy remains combined hormonal contraception.

Background

Approximately 3 million women in the United States have inherited bleeding disorders (1). Von Willebrand disease is the most common inherited bleeding disorder, with a prevalence of 0.6–1.3% (2, 3). Among women with menorrhagia, the prevalence is greater, and ranges from 5% to 15%. In particular, von Willebrand disease appears to be more prevalent among Caucasians with menorrhagia (4). One study suggests that 15.9% of Caucasians were found to have von Willebrand disease, compared with 1.3% of African Americans (5).

Von Willebrand disease is an autosomally inherited congenital bleeding disorder involving a qualitative or quantitative deficiency of von Willebrand factor (vWF). Dominant and recessive patterns of transmission exist. Von Willebrand factor is a protein that is critical for proper platelet adhesion and protects against coagulant factor degradation. There are three main types of von Willebrand disease. Type 1 (deficiency of vWF), the most common, usually is mild; type 2 (abnormal vWF) is less common; type 3 (complete absence of vWF) and pseudo von Willebrand forms are rare, and the presentation signs and symptoms are variable (6).

Presenting Symptoms and Signs

The most commonly reported symptom among women with a diagnosis of von Willebrand disease or suspected bleeding disorder is menorrhagia, but additional symptoms or signs also may be present (7, 8). Other presenting symptoms may include epistaxis, bleeding after dental extraction, bleeding from minor cuts or abrasions, postoperative bleeding, gingival bleeding, easy bruising, postpartum hemorrhage, joint bleeding, and gastrointestinal bleeding (7, 9). Among women with a diagnosis of von Willebrand disease, 48% reported easy bruising, 44% reported epistaxis, 51% reported gingival bleeding, and 84% presented with menorrhagia (8, 10). In one cross-sectional study, women with von Willebrand disease were also more likely than controls to report other gynecologic conditions, including ovarian cysts (52%), endometriosis (30%), leiomyomas (32%), endometrial hyperplasia (10%), polyps (8%), and hysterectomy (26%) in addition to menorrhagia (8).

Up to 20% of women presenting with menorrhagia at any time in life will have an underlying bleeding disorder (2, 4, 5). 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 menorrhagia at menarche was the most common initial bleeding symptom, occurring in 53% of women (11). The American College of Obstetricians and Gynecologists recommends that an initial reproductive health visit occur between the ages of 13 years and 15 years. This gives many clinicians an oppor-

tunity to inquire about menstrual history early in reproductive life (12). This also provides an opportunity to discuss the use of a menstrual calendar to aid in patient recall, which allows for clinicians to better differentiate menorrhagia from irregular, anovulatory bleeding. Anovulatory bleeding is more common during early adolescence and generally does not raise suspicion of a bleeding disorder (13, 14). Other screening tools for identifying women with menorrhagia who should be evaluated for a bleeding disorder include the pictorial bleeding assessment chart. This tool is useful for women to specifically record the number of pads or tampons used during their menstrual periods as well as noting how many times they may have passed clots or had flooding accidents. This tool has been validated in adult women and demonstrates greater than 80% sensitivity and specificity for scores greater than 100 (15). When the pictorial bleeding assessment chart tool is combined with a set of eight questions that focus on bleeding history, the sensitivity increases to 95% for diagnosis of any underlying bleeding disorder and 92% for von Willebrand disease; specificity is 72% and 8%, respectively (16).

A recent study also highlights the varied presentation of menorrhagia among women with von Willebrand disease of different age groups (5). One-hundred fifteen women of all ages with diagnoses of menorrhagia were evaluated for bleeding conditions. Nearly 50% of these women were ultimately determined to have platelet dysfunction, von Willebrand disease, or coagulation factor abnormalities. Importantly, bleeding disorders were found to be just as prevalent in adolescents as they were in adult women (5). The evaluation and management of women presenting with abnormal uterine bleeding have been addressed in other College publications as well (14). Nonetheless, inherited and acquired disorders of coagulation and hemostasis should be considered in the differential diagnosis of menorrhagia and abnormal uterine bleeding regardless of age.

Diagnosis

The first step in the evaluation of women with suspected bleeding disorders involves careful history and physical examination (9, 17). Directed questions are useful in assessing risk for inherited bleeding conditions (see Box 1) (9, 17). If red flags exist, then health care providers should follow the National Heart, Lung, and Blood Institute guidelines (9, 17). Family history of menorrhagia or other bleeding problems is helpful in assessing the need for further evaluation, even in the absence of a known bleeding disorder diagnosis. In one study of 580 women with menorrhagia, 33.9% of women had a family history significant for excessive bleeding, but less than 1% reported knowing of a specific or known or diagnosed bleeding condition within their families (5). Other important initial questions include personal history of bleeding problems, liver or kidney disorders, family history of hysterectomy at an early age, history of postpartum hemorrhage, or use of anticoagulants. Positive responses to initial questions should be followed by more probing questions and physical examination. Physical examination findings suggestive of a bleeding disorder include petechiae, ecchymoses, skin pallor, or swollen joints, although absence of these signs does not exclude the possibility of an underlying bleeding condition (7, 18, 19).

Box 1. Bleeding Disorder Red Flags

- Patient has a relative with an inherited bleeding condition
- Prolonged bleeding, lasting more than 15 minutes, from small injuries or wounds
- Heavy prolonged and recurrent bleeding following surgical procedures
- Bruising with minimal or no trauma with palpable lump under the bruise
- Spontaneous nosebleeds
- Prolonged bleeding following dental procedures
- Blood in the stool or bleeding ulcer that required urgent medical attention for cessation
- History of anemia requiring blood transfusion
- Heavy menses resulting in anemia or low iron stores
- Passing clots more than 1 inch diameter with menses or soaking more than one pad or tampon hourly
- Heavy bleeding during or following childbirth

Adapted from the National Heart, Lung, and Blood Institute, The Diagnosis, Evaluation, and Management of von Willebrand Disease. NIH Pub. No. 08-5832. December, 2007.

In patients with a positive screening history, laboratory testing is indicated (see Fig. 1) (9, 17). Initial tests should include complete blood count with platelets, prothrombin time, and partial thromboplastin time (fibrinogen or thrombin time are optional); bleeding time is neither sensitive nor specific, and is not indicated. Depending on the results of initial tests, or if a patient's history is suggestive of an underlying bleeding condition, specific tests for von Willebrand disease, including von Willebrand-Ristocetin cofactor activity, von Willebrand factor antigen, and factor VIII may be indicated (see Fig. 1) (9, 17, 19–21). These test results may be affected by several variables such as age, race, family history, blood type, stress, concurrent heavy bleeding, inflammation, exogenous or endogenous hormones, pregnancy, time of the menstrual cycle, sample processing, and quality of the laboratory (9, 17, 19–29). Because existing laboratory assays have limitations and no single diagnostic test reliably identifies the condition, this testing can be done in conjunction with a hematologist if necessary (9, 17). Furthermore, although certain types of von Willebrand disease may be easily distinguished from other bleeding

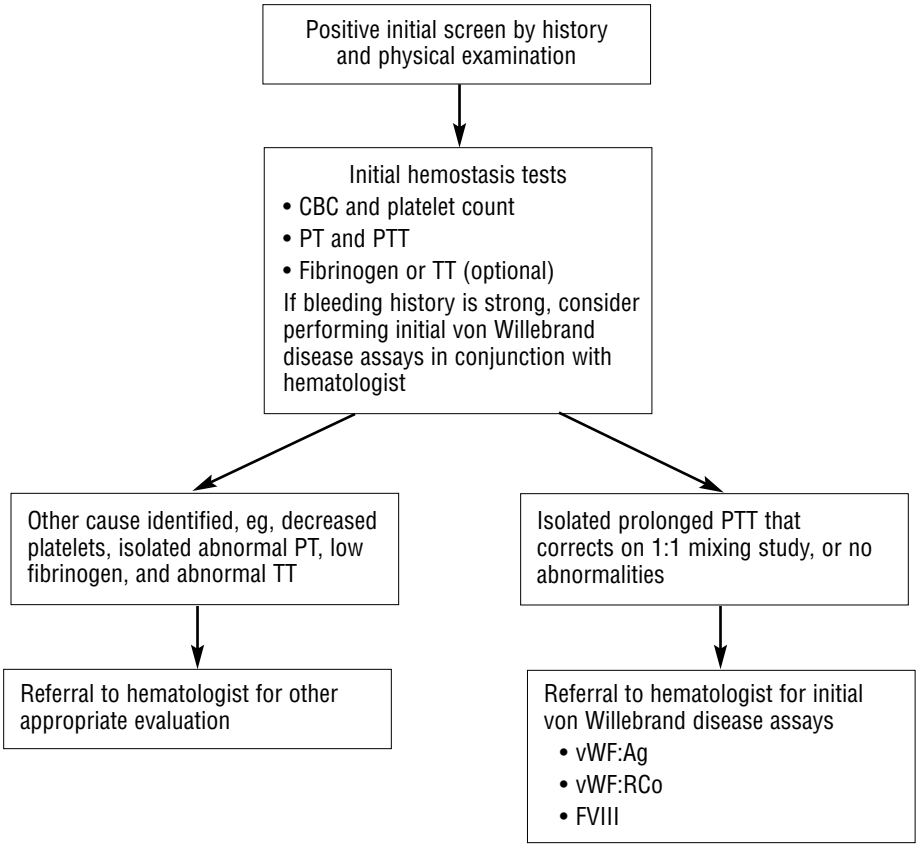

Fig. 1. Laboratory tests for suspected bleeding disorders. Abbreviations: CBC, complete blood count; FVIII, factor VIII activity; PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time; vWF:Ag, von Willebrand factor antigen; vWF:RCo, von Willebrand factor ristocetin cofactor activity. (Adapted from the National Heart, Lung, and Blood Institute, The Diagnosis, Evaluation, and Management of von Willebrand Disease. NIH Pub. No. 08-5832. December, 2007.)

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 (9, 17).

Management

Once a diagnosis has been established, a variety of treatments exist. Treatments include ways to increase endogenous plasma concentration of vWF, replace vWF, or promote hemostasis without affecting vWF. With mild von Willebrand disease and menorrhagia, combination hormonal contraceptives are first-line treatments. In a study involving women with a diagnosis of von Willebrand disease, 88% reported improvement in menorrhagia with oral contraceptives alone (7, 18). In addition, the levonorgestrel-releasing intrauterine device has been proved effective for the reduction of menorrhagia symptoms in adult women with bleeding disorders (30). Intrauterine devices containing levonorgestrel have been used in the adolescent population as well, especially in cases of traditional hormonal management failure. Although other contraceptives such as the contraceptive patch and contraceptive ring have not yet been studied in this population, theoretically, they would exhibit similar control of menstrual bleeding. Extended cycle combined hormonal contraceptives or depot medroxyprogesterone acetate are other options for consideration to help control heavy menses, although patients should still be warned about breakthrough spotting (14).

Newer hemostatic agents include antifibrinolytics, such as ε-aminocaproic acid and tranexamic acid (31). These are agents that inhibit the conversion of plasminogen to plasmin, inhibiting fibrinolysis, and thereby help stabilize clots. These agents also may be used alone or in conjunction with hormones to control menstrual bleeding, especially in the event a definitive diagnosis of von Willebrand disease has not yet been established. Because tranexamic acid is not yet approved for treatment of menorrhagia, this medication should be used with the guidance of a hematologist (9, 17, 31).

Therapies generally prescribed in conjunction with a hematologist once a diagnosis of von Willebrand disease-

has been established include desmopressin acetate and Recombinant Factor 8 and vWF complex infusion (9, 17). Desmopressin acetate is a synthetic derivative of the antidiuretic hormone vasopressin and works by stimulating the release of vWF from endothelial cells (21). Recombinant factor VIII and vWF complex infusion are a plasma-derived concentrate used to replace vWF and factor VIII. Patients also 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 (9, 17).

Special Considerations

Gynecologic concerns in women with von Willebrand disease include ruptured ovarian cysts, menstrual bleeding, endometriosis, and leiomyomas. Patients with heavy menstrual bleeding or hemorrhagic ovarian cysts may be easily managed with the introduction of a combined contraceptive regimen, by preventing both heavy menstrual bleeding or the development of hemorrhagic cysts (10). For the acute presentation of a ruptured ovarian cyst, patients with von Willebrand disease may require surgical intervention for hemostasis. In the presence of menorrhagia, patients with von Willebrand disease may require hormonal treatment (oral or intravenous) in addition to a hemostatic agent or desmopressin acetate and vWF replacement (9, 10, 17).

Obstetric concerns include postpartum hemorrhage, mode of delivery, operative delivery techniques, spontaneous abortion, and epidural management. Many experts have advocated that women with von Willebrand disease may have a vaginal delivery safely, with cesarean delivery reserved as indicated (9, 17). Because von Willebrand disease is an inherited condition, traumatic vaginal delivery, such as what may occur with the use of vacuum or rotational forceps, should be avoided because of the potential risk of traumatic injury to an infant with a possible hereditary bleeding disorder (32). If surgery is planned, it is important to coordinate care with a hematologist because vWF replacement may be necessary. The same considerations apply to epidural placement because this may be dependent on severity of disease; therefore, consultation with a hematologist is important. The rate of spontaneous abortion is similar to that of the general population. However, because patients may be at risk for hemorrhage at the time of spontaneous incomplete abortion, the use of vWF and factor VIII to control bleeding may be required (32). Furthermore, in a recent large epidemiologic study, the risk of postpartum hemorrhage for women with von Willebrand disease was 50% higher than for women without a bleeding disorder (29). Von Willebrand factor and factor VIII concentrates may be required to control bleeding in this situation as well (9). Once estrogen levels begin to decrease in the postpartum period, some individuals with bleeding conditions may present with delayed hemorrhage. Throughout pregnancy, at the time of delivery, and in the event of postpartum hemorrhage, vWF and factor VIII levels are important to assess because some women may require replacement of vWF and factor VIII for safe range maintenance (10, 32).

Any surgical procedure in a woman with von Willebrand disease requires consultation with a hematologist because of the potential risk of hemorrhage. Preprocedure vWF, vWF activity, and factor VIII levels may be important in determining the need for and timing of infusion treatment preoperatively and postoperatively (21).

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. Early warning signs and family history are critical for the acute treatment in these situations. Ensuring that families have adequate access to care and encouraging use of medical alert bracelets are important (9, 32).

Conclusion

Von Willebrand disease is a common cause of menorrhagia and other bleeding problems. Obstetrician–gynecologists should keep von Willebrand disease and other bleeding disorders in mind when evaluating patients with menorrhagia, especially at menarche. Once a diagnosis is made, collaboration with a hematologist is helpful for the long-term management of women with bleeding disorders such as von Willebrand disease. Von Willebrand disease affects the reproductive system as well as other body systems, so patients may need access to other health care providers in addition to gynecologists. Many resources exist for patients and health care providers through the National Heart, Lung, and Blood Institute, National Hemophilia Foundation's Project Red Flag, and the American Society for Hematology (9, 33).

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