Practical Hematologist

Recognizing and Treating von Willebrand's Disease in Women

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Introduction

Despite its recognition in 1926, clinicians struggle with the diagnosis and treatment of von Willebrand's Disease (VWD). Emblematically, Erik von Willebrand's index case was an adolescent woman—because VWD is the most common inherited bleeding disorder observed in women[1–3]*. Heavy menstrual bleeding (HMB) is the most common presentation in women with VWD.*[1,4] *Analysis of large patient claims data suggests there may be even more undiagnosed women with VWD. Accurately diagnosing VWD is imperative, as longitudinal retrospective analysis suggests that the recognition of VWD improves clinical outcomes.*[5,6]

Mary McGorray, MD, contributing author, recently asked Dr. Miguel Escobar, Professor at the McGovern School of Medicine at the University of Texas in Houston, and the National Hemophilia Foundation's 2021 Physician of the Year, to share his 25 years of experience in caring for women with VWD.

Dr. Escobar, why do women with von Willebrand disease escape clinical detection until they are often in crisis, such as menorrhagia or postpartum hemorrhage?

First, let's look at some statistics: As many as 1% of US women might have a bleeding disorder, meaning about 2 million women in the US could have a bleeding disorder. So, 15% to 30% of women that experience heavy menstrual bleeding may have a bleeding disorder. Yet, the number of women that get tested for bleeding disorder is quite small—about 2%.

Why do we think they escape detection? I think it is a lack of awareness at all levels. We are not doing enough education for our health care professionals, nor for the general population. We need to improve awareness regarding bleeding disorders.

If you look at all women, 30% of women report heavy menstrual bleeding (HMB). Certainly, not all those women are going to have bleeding disorders, but a great proportion of them will. The issue is: How do we educate these women as to what constitutes HMB? For many women, they may believe their periods are normal. An adolescent person may talk to her mom, and her mom may say "that's normal because it's normal for me, too!" Her mother may also have VWD and not realize what 'normal' menstrual bleeding means.

Many physicians, like pediatricians, primary care clinicians, emergency specialists, or OB/GYNs may lack awareness about bleeding disorders. For this reason, many women continue to have abnormal bleeding and undergo unnecessary procedures, like hysterectomies, simply because they have not been tested for a bleeding disorder!

Is von Willebrand's disease common?

It is common. When we get specific about VWD, it is the most common inherited bleeding disorder, an estimated 1% of the population. However, the numbers are much smaller when you describe *symptomatic* VWD.

What symptoms should prompt clinicians to dig deeper?

One important symptom is anemia! Many patients go to see their primary clinician or pediatrician with anemia, and it just doesn't capture the physicians' attention. There is *always* a reason why someone has anemia, especially iron deficiency anemia. This is quite common in women who have HMB.

Another symptom clinicians should be highly aware of is bleeding during pregnancy, especially in the postpartum setting. Patients with bleeding disorders have an increased risk of having postpartum hemorrhage (PPH). For OB/GYNs, this may be something they encounter commonly, but you must think of the possibility that a congenital bleeding disorder may be causing, or worsening, the symptoms of PPH.

Other symptoms we frequently encounter in patients with VWD are easy bruising, soft tissue hematomas, nose bleeds, and gum bleeding. While not specific to VWD, these symptoms should make you suspicious. It affects both males and females of all ethnic backgrounds.

Should the Bleeding Assessment Tool be part of every primary care practice or initial history?

Your best initial approach is to have a detailed history. We have tools that can be used to help us like the Bleeding Assessment Tool (BAT). This tool will guide you to ask specific questions about the bleeding history, including surgeries. BATs are accurate to distinguish between normal and abnormal bleeding. Family history is very important, because many bleeding disorders are hereditary– but, if they don't have a positive family history, that doesn't mean they don't have a bleeding disorder!

Regarding BATs, there is a self-administered version (the Self-BAT) that can be easily used by individuals with bleeding symptoms and has been validated for use as a screening tool for VWD. Now, if you ascertain a 'low' BAT score, but you still have a high clinical suspicion, you should still pursue a workup to rule out bleeding disorders.

Dr. Escobar, primary care physicians can be overwhelmed by tests for bleeding disorders. What tests should be ordered to correctly diagnose patients?

Screening tests like platelet count, prothrombin (PT) time, and partial thromboplastin time (PTT) are helpful, but patients with mild deficiencies of coagulation factors may not get picked up by these assays. Again, the personal and family history of bleeding is important to guide your workup.

If you still have a history that is quite significant, and, your screening tests are normal, you should perform additional testing which includes tests for von Willebrand's disease such as von Willebrand antigen, von Willebrand activity, factor VIII, factor IX, and factor XI—these specific coagulation assays look for mild deficiencies that you can miss with a screening test.

In patients who present with severe menorrhagia and iron deficiency anemia, what would be your first-line therapy, and, when should patients be considered for second-line therapies?

In my opinion every patient with HMB, with or without iron deficiency anemia, requires a workup for a bleeding disorder. This requires a multidisciplinary approach. Yes, you are the hematologist, but you need to work with the OB/GYN, and pediatrician or primary physician. Do your basic testing, including the screening tests, and possibly some additional testing for VWD and other deficiencies. If the patient has evidence of iron deficiency, your options are treating with oral iron, or even IV preparations, which we use frequently now, to increase their iron levels faster.

Options for HMB include antifibrinolytics, like tranexamic acid (TA), which is quite effective. If there is evidence that this patient has VWD, we can make choices ranging from desmopressin (DDAVP) in some instances, or using factor replacement during their menstrual periods, if necessary.

What about when patients are considering conception, do you make changes to therapy choices?

For many of these women we try to avoid the use of DDAVP (desmopressin) during pregnancy. Once they are able to get pregnant, if there is bleeding throughout the pregnancy, then we will consider the use of factor replacement. There is not a lot of literature regarding the use of antifibrinolytics (TA) during pregnancy. In certain circumstances we have used it, especially in very rare bleeding disorders where it is strictly necessary to block the fibrinolytic system.

Is factor replacement safe when women are trying to conceive or have conceived?

Theoretically it should be safe. I don't think there is data concerning the use of factor replacement and pregnancy. We do use it quite commonly in our women patients who are pregnant or undergoing delivery.

If you have a patient with a severe postpartum hemorrhage, what are guideline-driven recommendations for managing her next pregnancy?

PPH is frequently encountered by OB/GYNs. You need a multidisciplinary approach. First decide if the patient has a bleeding disorder or not, either acquired or congenital. One of the main approaches to PPH is the use of antifibrinolytics, TA.

In patients with VWD, for their future, we need to plan to prevent excessive bleeding with either the use of factor replacement and/or the use of antifibrinolytics during the delivery and postpartum.

So, when PPH occurs, use TA right away and hope for vasoconstriction and stopping the bleeding?

Correct. Many of these women, when they go into PPH can develop a coagulopathy very rapidly. You must monitor other parameters like fibrinogen, platelet count, and their coagulation factors. It is a multidisciplinary approach—you must act very quickly because these patients can get sick, very fast.

Is there room for the acute use of either plasma-derived von Willebrand (pdVWF) or recombinant von Willebrand factor (rVWF) in urgent hemorrhages? Let's say an OB/GYN is unaware a patient has a bleeding disorder, and the patient starts bleeding, is there a reason to start a pdVWF or rVWF?

If a patient does ***not*** have the diagnosis of VWD, I would not use it. If they do have VWD, and are experiencing a PPH, I think either of these products could be helpful. One of the main differences between those two products is that pdVWF has factor VIII, while rVWF only has VWF. If you have the luxury of measuring their levels then you certainly can choose between one product or the other, but sometimes in the acute setting, that is impossible to do.

What are the differences between VWF concentrates, and is there ever a time when pdVWF is preferable to rVWF?

pdVWF are factor concentrates derived from donors. These are very safe products. They have gone through different steps for removal of pathogens. rVWF has no human proteins in it. Regarding the components, pdVWF carries factor VIII and VWF, while rVWF has only VWF. If, for example, your patient has low factor VIII, say 40%, you might want to consider using pdVWF. But you could use rVWF and give additional factor VIII to increase factor VIII, to stabilize the VWF, or to maintain levels of both. If you already have factor VIII levels that are normal you might consider using only rVWF, because you don't want to increase factor VIII levels too highly, especially for a prolonged period, because you could make that patient prothrombotic.

Are there certain phenotypes of VWD that you might choose pdVWF rather than rVWF?

As you said, there are different types of vWF, but I don't know that you would choose one VWF concentrate over the other, because there are so many variables that play a role here…you might want to base it on what your levels of factor VIII are. If those factor VIII levels are quite low, then you could consider using a pdVWF. You also have to take into consideration the ratio between VWF and FVIII, when it comes to plasma derived VWFs.

In women with a PPH or with menorrhagia, how do you dose pdVWF and rVWF? What is our goal of therapy for prophylaxis?

For prophylaxis, the idea is to minimize the amount of bleeding. We must base our management on the data that is available from the clinical trials. You could consider looking at the target levels. If you have a mild to moderate bleed, then you can use doses between 20 to 40 units per kilogram (kg), and, you want to have your peaks probably above 50%. Depending on the type of bleed, you can treat for one to three days, or more.

If you have a severe bleed, you certainly want to go to a higher dose, like 50 units/kg, and achieve a peak of greater than 100% of FVIII/VWF. Then, after that, you may want to have trough levels above 50%. The duration of treatment is going to be based on how severe the bleed is. It's important to individualize treatment. Clinicians should follow these patients closely and make changes as needed for each patient.

We have a young woman who has had a difficult time with menorrhagia, and she's living at a hemoglobin of 7 g/dL or 8 g/dL and has a poor quality of life. How should we dose her for her menstrual period?

If she has von Willebrand disease, you can treat her by giving prophylaxis with a VWF concentrate during her periods. New guidelines for patients with severe and frequent bleeds suggest 'long-term' prophylaxis. You can give VWF concentrate, two to three times per week, to decrease, or even stop, the amount of bleeding.

All your clinical decisions will be based on bleeding symptoms tailored to each patient. You can treat during their menstruation. Every patient is going to be different. You could treat daily, or you might be able to treat every other day. In addition to that, it will be important to look at the possibility of using TA or aminocaproic acid to reduce the amount of bleeding. The concomitant use of estrogens is also another option for treatment.

Dr. Escobar, are patients' administering treatment at home, or does it require an infusion unit?

Most of the patients are treated at home. TA is available in a pill, so they can take it by mouth. Aminocaproic acid is either in liquid form, or pills. Factor replacement therapy is done intravenously. The hemophilia treatment centers usually will teach or educate the patients, and their caregiver, to be able to treat them at home. If the patient is unable to achieve this, we will send nursing services into the home to help them. Most patients can treat themselves with no problem.

Summary

Women living with VWD are high-risk stakeholders in the management of menorrhagia and postpartum hemorrhage.[7–12] They are at increased risk for severe morbidity and mortality from menorrhagia or PPH beyond the 'everyday' risks of GI bleeds, joint bleeds, and oral mucocutaneous bleeds that all VWD patients can experience. VWD's varying clinical phenotypes, and a dizzying array of tests that depend on accessibility and high levels of interpretive expertise, can discourage first-line clinicians' confidence in their ability to diagnose, manage, and guide their patients. We thank Dr. Miguel Escobar for his clarity and guidance in helping frontline clinicians diagnose and manage their patients at risk for the diagnosis and clinical consequences of VWD.

References

1. James AH. Women and bleeding disorders. *Haemophilia*. 2010;16(Suppl 5):160-167. doi:10.1111/j.1365-2516.2010.02315.x
2. James AH. Von Willebrand disease in women: awareness and diagnosis. *Thromb Res*. 2009;124(Suppl 1):S7-10. doi:10.1016/S0049-3848(09)70151-3
3. Nilsson. Commentary to Erik von Willebrand's original paper from 1926 'Hereditär pseudohemofili.' *Haemophilia*. 1999;5(3):220-221. doi:https://doi.org/10.1046/j.1365-2516.1999.0320a.x
4. James AH. More than menorrhagia: a review of the obstetric and gynaecological manifestations of von Willebrand disease. *Thromb Res*. 2007;120(Suppl 1):S17-20. doi:10.1016/j.thromres.2007.03.012
5. Sidonio RFJ, Zia A, Fallaize D. Potential Undiagnosed VWD Or Other Mucocutaneous Bleeding Disorder Cases Estimated From Private Medical Insurance Claims. *J Blood Med*. 2020;11:1-11. doi:10.2147/JBM.S224683
6. Sidonio RF, Haley KM, Fallaize D. Impact of diagnosis of von Willebrand disease on patient outcomes: Analysis of medical insurance claims data. *Haemophilia*. 2017;23(5):743-749. doi:10.1111/hae.13292
7. ClinicalTrials.gov: NCT04146376. Von Willebrand Factor in Pregnancy (VIP) Study (VIP). https://clinicaltrials.gov/ct2/show/NCT04146376?term=prophylaxis&cond=VWD+-+Von+Willebrand%27s+Disease&draw=3&rank=17<
8. Ragni M v. Blood volume-based von Willebrand factor to prevent postpartum hemorrhage in von Willebrand disease. *Blood Adv*. 2017;1(11):703-706. doi:10.1182/bloodadvances.2017005090
9. Ragni M v. Minimize Menorrhagia in Women With Von Willebrand Disease (VWDMin). *Clinical Trials.gov*. https://clinicaltrials.gov/ct2/show/NCT02606045?id=NCT03734588+OR+NCT02606045&draw=2&rank=2&load=cart
10. Machin N, Ragni M v. Recombinant vs plasma-derived von Willebrand factor to prevent postpartum hemorrhage in von Willebrand disease. *Blood Adv*. 2020;4(14):3234-3238. doi:10.1182/bloodadvances.2020002046
11. Ragni M v, et al. Prevent Postpartum Hemorrhage in Women With Von Willebrand Disease: The VWD-WOMAN Trial. *Clinical Trials.gov*. https://clinicaltrials.gov/ct2/show/NCT04344860?cond=VWD+WOMAN&draw=2&rank=1
12. Ragni M v, Machin N, Malec LM, et al. Von Willebrand factor for menorrhagia: a survey and literature review. *Haemophilia*. 2016;22(3):397-402. doi:10.1111/hae.12898

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