Von Willebrand Disease—Specific Aspects in Women

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Hamostaseologie 2022;42:330–336.

Abstract

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, which results from a deficiency or dysfunction of von Willebrand factor (VWF). The major symptoms of patients affected by VWD include mucocutaneous and gastrointestinal bleeding, easy bruising, and prolonged provoked bleeding due to injury or surgery. Although women and men are equally likely to be affected by VWD, women continue to be disproportionately affected by the bleeding challenges. Women with VWD suffer from sex-specific symptoms, such as menorrhagia, and are at higher risk of reproductive problems and recurrent miscarriage. Furthermore, pregnant women with VWD are more likely at higher risk of suffering from primary and secondary peripartal hemorrhage and anemia and the need for transfusions. Despite being affected by gynecologic and obstetrical bleeding, women face multiple barriers in obtaining an accurate diagnosis. This constitutes a problem that needs to be addressed, and early appropriate medical care should be ensured. There are several effective treatment options for women with VWD that can significantly improve their quality of life, including desmopressin, VWF concentrates, hormonal therapy, and antifibrinolytic therapy. During pregnancy, the monitoring of VWF activity levels is essential. The peripartal management depends on the type of VWD and on the measured levels of VWF levels and activity prior to delivery.

Keywords

- inherited bleeding disorder
- pregnancy
- von Willebrand disease
- heavy menstrual bleeding

Case Report (Part 1)

A 17-year-old woman sought medical attention from her general practitioner for heavy menstrual bleeding (HMB). During her menstruation, the young woman suffered from severe pain and heavy bleeding on days 2 to 4. In school, she had to change her sanitary protection at least five times daily to avoid the bleeding soaking through her clothes. Furthermore, the young woman felt tired, especially in the morning and during exercise. Her family explained her excessive bleeding as a "heavier variant of menstruation." During school sports she collapsed and was admitted to the hospital.

Introduction

Von Willebrand disease (VWD) is the most common inherited bleeding disorder resulting from a deficiency or dysfunction of von Willebrand factor (VWF), an elongated, multimeric protein with binding sites for platelets, collagen, and coagulation factor VIII (FVIII).[1] VWF has an integral role in hemostasis because it binds to and stabilizes FVIII as well as facilitates platelet adhesion to the injured endothelium. VWD has been characterized into three types[2]: type 1, the most common subtype, is observed in over 75% of cases and is caused by a partial quantitative deficiency of VWF.[3] Based on the American Society of Hematology (ASH) 2021 guidelines on the diagnosis of VWD, VWD patients with a bleeding phenotype and patients who have a VWF activity level between 30 and 50% are also classified as having VWD.[4] Patients with VWF activity less than 30% should be diagnosed as VWD regardless of bleeding symptoms. Type 2 VWD is observed in approximately 20% of cases and results from VWF dysfunction due to qualitative abnormalities. Type 2 VWD has been further subdivided into four subtypes. While type 2A is characterized by a loss of high-molecular-weight VWF, type 2B results from a change in the VWF structure

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received
February 8, 2022
accepted after revision
July 1, 2022

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Rüdigerstraße 14,
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DOI https://doi.org/10.1055/a-1891-9976.
ISSN 0720-9355.

leading to an increased affinity to platelets. Type 2M is caused by a reduced interaction of VWF with platelets, and type 2N results from reduced binding capacity of VWF to FVIII. Type 3, the rarest form, occurs in less than 1% of cases and is due to a virtual absence of VWF.[5] The major symptoms that are present in patients involve mucocutaneous and gastrointestinal (GI) bleeding, including epistaxis, easy bruising, and HMB, as well as provoked bleeding due to injury, surgery, and other invasive procedures, especially dental work.[6] HMB is defined as loss of more than 80 mL of menstrual blood per cycle, which in clinical practice remains difficult to determine. In previous studies, needing to change the sanitary protection more often than every 2 hours, bleeding that soaks through pajamas and/or sheets at night, and iron deficiency anemia were all correlated with HMB.[7] Studies of women affected by VWD have demonstrated that approximately 50 to 92% of women with VWD experience HMB.[8] Conversely, the prevalence of bleeding disorders among women with HMB is high with 5 to 24%.[9]

Although women and men are equally likely to be affected by VWD, women continue to be disproportionately affected by the bleeding challenges associated with menstruation and childbirth and are therefore twice as likely to be diagnosed as men. In the network of U.S. comprehensive hemophilia treatment centers, the age-adjusted prevalence of VWD was twice as high in women as in men for type 1 VWD and was similar between men and women for types 2 and 3. The incidence of type 1 has increased over the observation period of 8 years and has been nearly threefold higher for women than men (26.2 vs. 9.9/100,000). However, the peak prevalence has varied by sex, and the peak prevalence of VWD is at ages 5 to 14 years in males and at ages 15 to 24 in females.[9]

Despite the fact that women are more likely to be diagnosed with VWD due to their early onset of bleeding symptoms, an accurate and timely diagnosis remains a challenge, and affected women may experience delays of up to 15 years or more from the onset of bleeding symptoms to a VWD diagnosis.[3,9,10]

Independent of the severity of the bleeding, women also had a significant diagnostic delay in comparison to men.[3]

Several case reports and series have pointed out that there might be an increased risk of recurrent miscarriage in VWD patients, but the etiology has not been fully clarified.[11–13] Furthermore, VWF is known to regulate angiogenesis by influencing molecular pathways such as integrin αvβ3, angiopoietin-2, and galectin-3.[14] These pathways have a role as the master regulators of angiogenesis, endothelial homeostasis, and vascular endothelial growth factor (VEGF) signaling. In vitro and in vivo studies have shown that a lack of VWF leads to enhanced vascularization and consequently to ischemia. Conversely, upregulation of VWF expression by angiogenic factors was reported to be present in the tumor microenvironment. Anti-VEGF treatment with bevacizumab was shown to decrease the plasma levels of VWF.[15]

Since deficiencies of VWF are associated with pathological angiodysplasia and vascular malformations that account for GI angiodysplasia and bleeding, the predisposition for angiodysplasia accounting for recurrent miscarriage has been considered as well.[14,16–18] The treatment options for bleeding complications in patients with VWD include desmopressin (DDAVP), the administration of VWF concentrates including both plasma-derived and recombinant products, as well as antifibrinolytic therapy (e.g., tranexamic acid, TxA).[19] After giving DDAVP, the mobilization of stored VWF is achieved within 30 to 60 minutes to reach increased plasma FVIII and VWF levels, which usually last for 6 to 8 hours.[20] DDAVP is generally well tolerated, safe, and cost-efficient. Side effects of DDAVP administration include hyponatremia, hypotension, tachycardia, nausea, and malaise.[21] In type 2B VWD, DDAVP is contraindicated due to the potential aggravation of thrombocytopenia, and there is no response expected in type 3 VWD patients.

Prior to a prescription of DDAVP, a test-dose infusion at the time of diagnosis is highly recommended to establish the dynamics and duration of the response, as well as to determine the patient's tolerance to DDAVP. The side effects of DDAVP application include mild tachycardia, flushing, and headache, which are attributable to the vasomotor effect of DDAVP.[22] TxA reduces bleeding by inhibiting endometrial clot-degrading enzymes. The patients' bleeding history, the severity of the patient's bleeding and injuries, the patient's interventions or surgery, and the patient's VWD subtype should be considered in the treatment and prophylaxis of VWD. Furthermore, assessing the response to previous therapies in terms of any bleeding events that occurred despite the substitution of VWF concentrates is essential when determining further recommendations.

The ASH 2021 guidelines on the diagnosis and management of VWD encourage the role of long-term prophylaxis in patients with VWD.[19] Especially in patients with a history of severe and frequent bleeds, the application of long-term prophylaxis is recommended to reduce and prevent recurrent mucosal bleeds. The role of long-term prophylaxis should be assessed in affected women with HMB, and intermittent periodic prophylaxis should also be considered.[19,23] Relevant answers to the questions addressed by the VWD panels in the 2021 ASH guidelines on gynecological and obstetric management are displayed in ►Tables 1 and 2. The tables summarize key recommendations regarding prophylaxis for frequent recurrent bleeding, management options for HMB, management of VWD in the context of neuraxial anesthesia during labor and delivery, and target VWF and FVIII activity levels for peripartal interventions. Furthermore, they include recommendations on the management in the postpartum period.

Heavy Menstrual Bleeding and Other Reproductive Conditions

HMB is the most common bleeding symptom in women with VWD, and HMB occurs monthly with significant morbidity, which includes the development of symptomatic iron deficiency anemia, psychological distress, and reduced quality of life.[24] Furthermore, HMB is associated with lifestyle

Table 1 Recommendation on the management of heavy menstrual bleeding (HMB) in VWD patients; adapted from Connell et al[19]

Recommendation on the management of heavy menstrual bleeding (HMB) in VWD patients
• Women who do not wish to conceive: use of hormonal therapy (combined contraceptive pill or levonorgestrel-releasing intrauterine system) or tranexamic acid is recommended over desmopressin.
• Women who wish to conceive: use tranexamic acid over desmopressin
• Desmopressin is not effective in type 3 and many type 2 VWD patients and is contraindicated in type 2B VWD.
• Combination therapy might be necessary if the initial treatment is insufficient.
• The role of prophylaxis should be considered.
• Additional treatment for the first several menstrual cycles after the placement of a levonorgestrel-releasing intrauterine system may be required and should be considered.
• Use of hormonal therapy might be considered beneficial for the treatment of menstrual pain and for the management of endometriosis and polycystic ovary syndrome.
• Iron deficiency anemia is associated a diminished health-related quality of life and should be treated.
• Affected women should undergo a standard gynecologic exam to rule out common pelvic pathologies, such as fibroids and polyps.
• Special attention is required in patients who are at high risk of endometrial hyperplasia/malignancies (women age >35 years, with polycystic ovaries, a high body mass index, and comorbidities, such as diabetes and hypertension).

Abbreviation: VWD, von Willebrand disease.

Table 2 Recommendation on obstetric management in VWD; adapted from Connell et al[19]

Recommendation on obstetric management in VWD
• Monitor the VWF and FVIII activity levels during the third-trimester and generate a plan for anesthesia and delivery in case of replacement of factor concentrates.
• Use VWF:activity target of 0.50–1.50% over >1.50% for neuraxial anesthesia during labor and pregnancy.
• VWF activity levels should be maintained at 0.50% while an epidural catheter is in place and should be maintained for at least 6 hours after its removal.
• Decisions regarding anesthesia and delivery should be made in advance of the patient's due date and with the help of a multidisciplinary team (anesthesia, hematology, and obstetric), and the team should respect the patient's will.
• Vaginal delivery or caesarean section can be performed when the VWF:RCo activity is maintained >50% and the platelet count should be maintained at $>50 \times 10^9$/L (2C).
• Patients should also be assessed for the thrombotic risk post-delivery, and thromboprophylaxis should be provided.
• The use of tranexamic acid for 10–14 days during the postpartum period reduces the risk of secondary PPH and is recommended.
• Tranexamic acid may be given systemically via the oral or IV route (oral dose is 25 mg/kg (typically 1,000–1,300 mg) three times per day for 10 to 14 days or longer if the blood loss remains significant.

Abbreviations: FVIII, factor VIII; IV, intravenous; PPH, postpartum hemorrhage; VWD, von Willebrand disease.

disruptions, such as work and school absenteeism, and increased health care costs.

Using a validated bleeding-assessment tool, as an initial screening test is essential to determine the need for more specific blood testing when diagnosing bleeding disorders, especially in the primary care setting. The International Society on Thrombosis and Haemostasis (ISTH) Bleeding Assessment Tool (ISTH-BAT) is currently the most widely recommended and used scoring tool in clinical practice.[25]

Philipp et al developed a short eight-question screening instrument that targets women with unexplained menorrhagia to stratify them in the primary care setting for further referral and testing. This questionnaire is based on the bleeding symptoms that are present in women with VWD; it includes four criteria; and the screening tool is positive if one of four criteria was met. The criteria include the severity of HMB, the history of anemia treatment, bleeding episodes after dental surgery, the history of delivery and general surgery, as well as the family history of bleeding disorders.[26]

In addition to HMB being a major symptom, it is not the only reproductive challenge that women with VWD are at a higher risk for. A significantly higher incidence of hemorrhagic ovarian cysts, endometriosis, and endometrial hyperplasia[27,28] was previously reported in affected women. Hemorrhagic ovarian cysts may result from bleeding into the residual follicle at the time of ovulation, which potentially leads to intraperitoneal bleeding and the need for surgical intervention.[3,10,28,29] Endometriosis, a chronic condition affecting 5 to 10% of women of reproductive age in which endometrial tissue is present outside of the uterus, was more likely to be detected in women with VWD.[28,30,31] Clinically, endometriosis is associated with severe cyclic pain, dysmenorrhea, dyspareunia, and dysuria and can

result in chronic inflammation, debilitating pain, and infertility. Interestingly, the prevalence of endometriosis is increased in females with subfertility. Retrograde menstruation, which constitutes one explanation for the pathogenesis of endometriosis, may be more common in women with HMB. Therefore, it is suspected that women with HMB are prone to suffer from retrograde menstruation, which might facilitate the development of endometriosis.[3,27,28]

Since women affected by VWD are more prone to reproductive problems, the identification, as well as prompt attention given to the abovementioned symptoms, is essential to deliver adequate treatment and to prevent it from becoming chronic.

In terms of the treatment of HMB, the first choice of treatment should be hormonal therapy that consists of a levonorgestrel-releasing intrauterine system or with combined oral contraceptives, followed by TxA during HMB and DDAVP.[7,9,32] Hormonal therapy has been shown to be effective in controlling HMB based on data from women who do not have bleeding disorders.[7] DDAVP can be administered through the intranasal route, with recommended fixed doses of 300 µg in women of $\geq$50 kg body weight and150 µg in those $<$50 kg. By administering DDAVP during the first 3 days of each menses, the menstrual bleeding can be effectively normalized.[33]

Previous evidence has suggested that TxA significantly reduces the amount of menstrual blood loss per menstrual cycle and improves quality of life for affected patients.[6,7,34,35] The recommended oral dosage of TxA for HMB is 1 g three times a day for up to 4 days.[34–36] In patients with type 3 VWD and in women with severe and not otherwise controllable HMB, the prophylactic administration of VWF/FVIII (40 IU VWF/kg/d) during the first 3 days of each period can normalize menstrual bleeding.[37]

Pregnancy

Pregnancy is associated with a physiological rise in the VWF levels and FVIII levels, which is considered to contribute to improved hemostasis and the preparation for delivery. Due to the physiological increase in procoagulant factors during pregnancy, pre-existing bleeding conditions and clinically relevant bleeding episodes remain particularly rare in patients with VWD type 1, as well as in affected women with VWF activities $>$50 (IU/dL).[38]

In previous studies, women with VWD were not at a higher risk of developing pregnancy complications, such as preeclampsia, eclampsia, abruption of the placenta, or intrauterine fetal growth restriction.[39] Women with VWD had a higher probability of undergoing cesarean delivery, which should be taken into consideration throughout the antepartal management and monitoring. Additionally, women with VWD were more likely to require transfusions due to blood loss. Women with VWD have had a longer hospitalization for childbirth.[27]

Furthermore, pregnant women with VWD were more likely to suffer from anemia and thrombocytopenia, which are probably explained by the increased bleeding tendency during and before pregnancy. In an observational study conducted by Majluf-Cruz et al, in which women with one or more episodes of postpartum hemorrhage (PPH) were compared with controls, the proportion of women suffering from VWD in the PPH group was significantly higher. Retrospectively, around 80% of women with PPH had clinical symptoms suggesting a hemostatic disorder, including HMB, which emphasizes the predictive role of HMB in preventing and treating PPH.[40]

Antepartal Management

Delivery represents a major hemostatic challenge for women with VWD who are at higher risk of developing PPH and who require transfusions, despite the increases in the plasma levels of FVIII and VWF during pregnancy.[41]

In the prenatal assessment, bleeding and the patient's family history should be considered. Additional bleeding disorders, such as FXIII deficiency, should be searched for and taken into consideration, since they might aggravate PPH. Furthermore, women with combined bleeding disorders might require combination of treatments. In general, peripartal therapy, such as replacement therapy, is rarely required prior to delivery for women with VWD type 1 who exhibit VWF ristocetin cofactor (VWF:RCo) $\geq$50% if no severe bleeding history is documented in the patient's medical history. The risk of bleeding has been shown to be minimal when the FVIII activity (FVIII:C) and VWF:RCo levels were higher than 50%.[6,16] Therefore, measuring the parameters within the third trimester ($\sim$32–34 weeks) and ahead of the expected date of delivery should be taken into consideration when considering the peripartal recommendations.

Furthermore, it is essential to perform blood count examinations, determine the hemoglobin levels of the patients, and screen women for iron deficiency. Since anemia constitutes a well-established risk factor for PPH and is associated with adverse fetal and maternal outcomes, women with iron deficiency should be treated with appropriate therapy.[42] In the case of bleeding complications, the restrictive use of DDAVP is recommended due to the possible side effects and interactions, the risk of fetal hyponatremia, and the adverse effects of preeclampsia. Since DDAVP has been known to interact with the oxytocin receptor, its use might promote uterine contraction. However, controversial recommendations exist because the application of DDAVP is practiced in the United Kingdom, both in pregnancy and at delivery.

For women with VWD, delivery should be planned in a specialized high-risk obstetric hospital that is affiliated with an obstetrician, a hematologist, an anesthetist, and a neonatologist and preferably in an institution that has an onsite hemostasis laboratory.[43,44] The required peripartal treatments and substitutions should be generated and sent to the obstetric hospital in time to avoid a delay in therapy.

Peripartal Management

PPH is defined as blood loss greater than 500 mL that occurs within 24 hours of delivery. Secondary PPH, in contrast to primary PPH, occurs between 24 hours and 6 weeks after

delivery. PPH represents 25% of all maternal deaths worldwide,[45] and postpartum and severe PPH, in addition to perineal hematomas, should be considered in women with VWD.[20,42,46–48]

The peripartal management depends upon the type of VWD and the measured levels and activity of VWF. Women with type 1 VWD with baseline VWF activity levels >0.3% are likely to obtain VMD activity levels that are within the normal range by the third trimester. In contrast, replacement therapy may be required (according to the measured activity levels and the bleeding severity) in women with type 3 VWD, type 2 VWD, or type 1 VWD with FVIII or VWF levels <50% or who have combined bleeding disorders and a positive history of severe bleeding. Women with VWD type 2 may reach normal VWF antigen (VWF:Ag) levels. However, since VWF is dysfunctional in affected women, replacement therapy may be required in women who have bleeding conditions (e.g., intermittent vaginal bleeding during delivery), and replacement therapy may be essential during delivery. Women with type 2B VWD do not benefit from the pregnancy-associated rise in VWF. However, thrombocytopenia may worsen in pregnancy. Therefore, platelet should be measured regularly during the third trimester to determine if the patient has thrombocytopenia and to monitor thrombocytopenia if it develops.[1,39,49] A platelet transfusion is recommended if the platelet count is $<50 \times 10^9$/L, and the administration of VWF/FVIII concentrates should be performed at the time of delivery. Women with type 3 VWD typically do not show any increase in the VWF levels, even in the last trimester.

To evaluate peripartum management strategies, a cohort study on 811 deliveries reported primary PPH in 32% and secondary PPH in 13% of women with VWD.[50] Surprisingly, the overall primary PPH incidence in the individual patient data was 34%, similar between women who received prophylactic treatment to prevent PPH and those who did not. Neonatal bleeding events were reported in 4.6% of deliveries. The authors concluded that there is an ongoing high risk for PPH, despite prophylactic treatment, and the need for higher quality evidence from larger prospective cohort studies to improve management strategies.

The management of obstetric analgesia and anesthesia in women with VWD requires an individualized risk assessment. The careful assessment of the patient's coagulation status and the presence of clotting factors and bleeding tendency during the third trimester should be performed. Epidural anesthesia can be recommended without additional hemostatic measures in women with VWF activity levels >50 IU/dL before delivery. Spinal anesthesia (e.g., peridural anesthesia) should not be performed without adequate replacement therapy in women with antepartum VWF activity levels <50 IU/dL or in those patients with a history of severe bleeding.[16,19,39,43] Furthermore, VWF levels of >50 IU/dL should be maintained for the duration of the catheter placement and prior to the removal of the catheter.

If replacement therapy is required, substitution of VWF/FVIII concentrates is recommended at a dose of 40 to 60 IU/kg of body weight during the late stage of labor and should be repeated once daily for at least 3 days, followed by the administration of oral TxA for a week. It is recommended to extend the substitution of VWF/FVIII concentrates (20–30 IU/kg) up to 5 to 7 days to possibly maintain the VWF levels at >50 IU/dL to reduce secondary PPH.[19] The VWF activity levels and the FVIII:C should be monitored once daily during the substitution. Further recommendations are summarized in ►Table 2.

After vaginal delivery, concentrates can be administered for 3 to 5 days, whereas after cesarean delivery, the administration of FVIII/VWF concentrates should be prolonged for at least another 5 days. The peripartal administration of VWF replacement might cause a prothrombotic situation. Therefore, FVIII overload should be avoided, and the administration of VWF products in patients with a low or no FVIII content is prudent.[16]

During delivery, bleeding complications may occur not only in women with VWD, but they can also potentially affect the child. In type 1 VWD, the bleeding risk is minimal and negligible, since increased VWF and FVIII activity levels have been demonstrated in healthy newborns.

In women with VWD who suffer from manifest PPH, TxA, intravenously 1 g, should be applied to decrease the excessive fibrinolytic activity, since there is increased systemic and local fibrinolysis. In women with confirmed PPH, the use of TxA reduced the risk of hysterectomy.[35–37,50,51] Thromboprophylactic treatment after cesarean section with low-molecular-weight heparin should be administered to patients to attenuate the risk of venous thromboembolism. Women with VWD are also at a higher risk of heavy lochia loss during the puerperium, since the pregnancy-induced rise in VWF and FVIII decreases within a few days after delivery. For an early detection of secondary PPH, the patient's blood loss should be documented up to approximately 14 days after delivery. In patients with secondary PPH or heavy postpartum flow (patients who have to change their sanitary protection more often than every 2 hours), referral to a hematologist is essential to determine the VWF levels. TxA can be recommended in patients with heavy postpartum flow[8,51] and can be safely prescribed to breastfeeding women.

The management of pregnant patients requires close surveillance to reduce the risk of bleeding. The monitoring and management of women with VWD during pregnancy and delivery mainly depends on the subtype of VWD, the activity levels of VWF, and the patient's bleeding history. The mere presence of VWD is not a reason to determine that a patient needs a cesarean section. The replacement treatment should be planned well ahead of delivery. Both the bleeding risk for the mother with VWD and the possibility of bleeding in an affected child must be considered during delivery. In postpartum management, the decrease in the VWF levels puts women at higher risk for secondary PPH. In addition to FVIII/VWF concentrates, antifibrinolytics play an essential role in the prophylaxis and treatment of PPH and for the treatment of excessive lochia.

The challenge in the obstetric management of women with VWD lies in avoiding overcautious management on the one hand and incautious management on the other hand. Adopting an overly reluctant management due to the fear of

bleeding complications and a lack of expertise might lead to avoiding treatment, such as for the application of neuraxial anesthesia or cesarean section, if required from an obstetrics point of view. This could lead to affected women not receiving adequate treatment, which includes adequate pain management. Conversely, the normalization or the rise in the VWF activity levels, which lead to a rare occurrence of relevant bleeding episodes during pregnancy, might entice clinicians to adopt incautious practice without close surveillance. To maintain the required balance between providing adequate obstetric management and pain control while adequately monitoring the patients, close cooperation with a hematologist is essential.

Case Report (Part 2)

Referring to the case presented, the patient's initial blood work in hospital included a hemoglobin of 9 g/dL (normal: 12–16 g/dL). Iron deficiency anemia was diagnosed because the patient's ferritin levels measured 6 ng/mL (normal: 9–140 ng/mL). The patient's prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal. Intravenous fluids were administered as well as an initial intravenous iron infusion. Furthermore, oral iron supplementation was initiated. In the emergency department, the young woman explained that she suffered from easy bruising when she was questioned about her medical history. She had no history of previous surgeries. The patient had no family history of bleeding disorders. After discharging the patient, she was referred for a hematologic consultation since menorrhagia was suspected. In the hematology department, the patient's calculated ISTH-BAT score was 9 ($\geq$6 is considered pathologic). Her PT and aPTT were within the normal ranges. Special coagulation blood work was performed: her VWF:Ag was 45 IU/dL (normal: 60–150%), her measured VWF:activity (ristocetin cofactor) was 38.5, and her FVIII:C was 60%. Her platelet aggregation testing was normal. Type 1 VWD was assumed. The patient was provided another appointment to perform further blood work and coagulation tests, as well as genetic testing, and eventually a DDAVP trial was arranged. Meanwhile, the patient was given TxA 1 g orally three times a day during menses for a maximum of 4 days. Furthermore, the patient was referred to the gynecologist to discuss hormonal therapy for managing her HMB.

Funding
None.

Conflict of Interest
F.E. declared no conflicts of interest.
W.M. has received fees from CSL Behring, LFB, Octapharma, and Takeda.

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