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How I treat low von Willebrand factor levels

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Partial quantitative deficiency of plasma von Willebrand factor (VWF) is responsible for the majority of cases of von Willebrand disease (VWD), the most common inherited human bleeding disorder. International consensus guidelines recommend that patients with reduced plasma VWF antigen (VWF:Ag) levels and bleeding phenotypes be considered in 2 distinct subsets. First, patients with marked reductions in plasma VWF levels (<30 IU/dL) usually have significant bleeding phenotypes and should be classified with "type 1 VWD." In contrast, patients with intermediate reduced plasma VWF levels (in the range of 30-50 IU/dL) should be considered in a separate category labeled "low VWF levels." These patients with low VWF commonly display variable bleeding phenotypes and often do not have *VWF* gene sequence variations. Because the pathophysiology underlying low VWF levels remains largely undefined, diagnosis and management of these patients continue to pose significant difficulties. In this article, we present a number of clinical case studies to highlight these common clinical challenges. In addition, we detail our approach to establishing a diagnosis in low VWF patients and discuss strategies for the management of these patients in the context of elective surgery and pregnancy. (*Blood*. 2019;133(8):795-804)

Introduction

von Willebrand disease (VWD) is caused by quantitative or qualitative deficiencies in plasma von Willebrand factor (VWF) and constitutes the most common inherited bleeding disorder.[1] Reduced plasma VWF levels, in combination with a family history of bleeding, have a reported prevalence of 1%.[2] Furthermore, significant bleeding symptoms due to reduced VWF levels have been observed in ~1 in 1000 of the normal population.[3,4] Type 1 VWD is responsible for the majority of cases and is characterized by a partial quantitative VWF deficiency. In recent years, understanding of the pathobiology underlying quantitative VWF deficiency has progressed significantly following a number of type 1 VWD cohort studies.[5-8] Consequently, more recent clinical guidelines from the National Heart, Lung, and Blood Institute, the European Group on von Willebrand disease, and the UK Haemophilia Doctors Organization recommend that patients with reduced plasma VWF antigen (VWF:Ag) levels and bleeding phenotypes should be considered in 2 distinct subsets.[9-11] Patients with marked reductions in plasma VWF levels (<30 IU/dL) usually have significant bleeding phenotypes and should be labeled "type 1 VWD."[9-11] These patients are likely to have identifiable *VWF* gene mutations and exhibit autosomal-dominant inheritance patterns.[7,12] In contrast, patients with intermediate reduced plasma VWF levels (30-50 IU/dL) should be considered in a separate category labeled "low VWF levels."[9] These patients with low VWF commonly display variable bleeding phenotypes and often do not have *VWF* gene sequence variations (Table 1).[7,13] Although the pathophysiology underlying low VWF levels remains poorly defined, recent data suggest reduced VWF synthesis and/or secretion from endothelial cells rather than enhanced VWF clearance.[13] Despite these advances, the diagnosis and management of these patients continue to pose significant difficulties. In this article, we present a number of clinical case studies to highlight these common clinical challenges. In addition, we detail our approach to establishing a diagnosis in low VWF patients and discuss strategies for the management of these patients in the context of elective surgery and pregnancy.

Diagnosis of low VWF

Case 1

A 26-year-old female with a history of heavy menstrual bleeding (HMB) is referred from the gynecology service for assessment of a possible bleeding disorder. She describes spontaneous bruising since childhood, with 5 to 10 bruises present on occasion. She required cauterization for epistaxis as a teenager and packing following a dental extraction (DE). Her periods have been heavy since menarche, lasting up to 8 days in duration, with pad changes every 1 to 2 hours on days of heaviest flow. She has used oral iron supplementation intermittently since the age of 14 years due to recurrent iron deficiency. Her mother and older sister also have HMB, resulting in her mother undergoing a hysterectomy at age 42 years. Both her mother and sister have easy bruising, and her sister required repeat presentation for suturing for bleeding following a DE.

Discussion of case 1

Previous studies have demonstrated that bleeding symptoms, such as epistaxis, easy bruising, and menorrhagia, are commonly reported in healthy controls.[14,15] Overall, these surveys suggest that the percentage of controls with ≥1 bleeding symptom could be conservatively estimated at ~25%.[16] Because the normal range for plasma VWF:Ag levels is 50 to 200 IU/dL, by definition, 2.5% of the normal population will also have VWF

Table 1. Differences between low VWF and type 1 VWD

	Low VWF	Type 1 VWD
Diagnosis	Plasma VWF levels consistently 30-50 IU/dL	Plasma VWF levels consistently <30 IU/dL
VWF gene sequence variations	Detected in 40% to 64% of patients	Detected in majority of patients (up to 91.8%)
Pathogenic mechanism	Predominantly due to reduced VWF synthesis/secretion within EC. Subtle enhanced clearance in some cases.	Depending upon *VWF* gene mutation, can be attributable to a major impairment in VWF synthesis and/or markedly enhanced VWF clearance (type 1C VWD)
Response to DDAVP	Consistent and reproducible plasma VWF responses, with levels sustained >50 IU/dL at 4 h	Variable responses, related to the nature of the underlying *VWF* mutation. Complete response, partial response, or failure to respond may be seen. In patients with type 1C VWD, VWF half-life may be <4 h.
Need for DDAVP trial	No need for routine DDAVP trial but confirm plasma VWF:Ag levels and duration of response at time of first therapeutic use	DDAVP trial should be performed and should include plasma samples at 4 h post-DDAVP to ensure no rapid fall-off in plasma VWF levels
Plasma VWF half-life	Some low VWF patients have elevated VWF:pp/VWF:Ag ratios consistent with subtly increased VWF clearance	Related to underlying *VWF* mutation, but patients with type 1C VWD may have markedly enhanced VWF clearance with half-lives <4 h
ABO effect	Blood group O is strongly overrepresented	The effect of ABO blood group is less significant
Impact of aging	Plasma VWF levels increase with age and often correct into the normal range (>50 IU/dL)	Depending on underlying VWF gene mutation, plasma VWF levels may increase with age, but often remain <50 IU/dL
	Not clear whether age-related VWF correction necessarily equates to resolution of bleeding phenotype	Unknown whether age-related increase in plasma VWF levels attenuates bleeding risk

levels < 50 IU/dL. These combined prevalence data mean that 0.6% of the general population coincidentally has bleeding symptoms and reduced VWF levels and highlight the significant risk for false-positive diagnosis of partial quantitative VWD in this context.[16] Consequently, in patients referred for investigation of possible low VWF, a systematic approach to the clinical assessment of bleeding phenotype and laboratory investigations (including VWF assays) is essential.

Objective assessment of bleeding history in diagnosis of low VWF

Initial assessment of this patient focuses on objective assessment of bleeding phenotype using a standardized bleeding assessment tool (BAT). Although a number of BAT iterations have been described, the 2 questionnaires most widely studied in VWD are the Condensed Molecular and Clinical Markers for the Diagnosis and Management of Type 1 (MCMDM-1) VWD score and International Society of Thrombosis and Hemostasis (ISTH) BAT score.[17-19] Previous studies have validated the use of both scores in the diagnosis of type 1 VWD.[19,20] Both BATs assess bleeding over a number of specific domains, including menorrhagia, cutaneous bleeding, and postoperative bleeding. The Condensed MCMDM-1 VWD score differs from the ISTH BAT score in that negative scores are applied for 2 hemostatic challenges without bleeding in the postoperative, dental, and postpartum domains.[19] As such, the threshold for positive scores differs between the BATs (≥4 for males and females for the Condensed MCMDM-1 VWD score; ≥4 for males or ≥6 for females using the ISTH BAT score).[19,20] Interestingly, recent studies have demonstrated that the ISTH BAT score may also be more sensitive than the Condensed MCMDM-1 score in assessing HMB.[21] This difference relates to the fact that the ISTH BAT includes HMB since menarche and that no score is accrued for the menorrhagia domain of the Condensed MCMDM-1 VWD score unless medical intervention is sought, irrespective of the patient's HMB symptom severity.[21] Many patients with significant menorrhagia may not appreciate the severity of their symptoms and, thus, fail to seek medical attention. As such, the ISTH BAT score is more sensitive to detection of menorrhagia because it includes assessment of the presence of clots, flooding, frequency of pad change, and the duration of symptoms.[18,21] Consequently, in our initial assessment of patients referred with possible low VWF, we use the ISTH BAT score over the Condensed MCMDM-1 VWD score for the objective initial assessment of bleeding phenotype. Based upon her significant bleeding history, an ISTH BAT score of 10 was calculated for our index case.

Although the utilization of BAT scores standardizes bleeding phenotype assessment in patients with low VWF, a number of important caveats should be considered. First, BAT scores should be assigned at first diagnosis whenever possible. If scores are being calculated retrospectively, only symptoms experienced prior to initial diagnosis should be included, because subsequent prophylactic treatments given for procedures may lead to falsely elevated scores.[17] Second, for younger patients or adults who have undergone a limited number of previous hemostatic challenges, the BAT score may be negative, even in the presence of an underlying bleeding diathesis.[17] Third, although the MCMDM-1 VWD score has been shown to predict future bleeding risk, recent data suggest that the ISTH BAT may not predict risk of surgical bleeding.[22,23]

Laboratory investigations in the diagnosis of low VWF

For patients with an abnormal BAT score, laboratory investigations should be performed to investigate for the presence of hemostatic defects. In addition, a complete blood count and ferritin levels should be assayed for all patients with a history of significant bleeding. For the bleeding state work-up, in our institution, we first assess prothrombin time, activated partial thromboplastin time, fibrinogen level, and VWF levels (VWF:Ag, WF ristocetin cofactor assay [VWF:RCo], VWF collagen binding [VWF:CB]). In patients with a marked bleeding phenotype, we proceed to assay clotting factor assays (factor II [FII], factor V, factor VII, factor VIII, factor IX, factor X, factor XI, and factor XIII), platelet aggregometry, and platelet nucleotide testing. Importantly, in low VWF patients with a marked bleeding phenotype, it is our practice to complete a full clotting factor screen and platelet-aggregation studies to exclude the possibility that additional coagulation defects may be present. Although this is rare,[13] it clearly has direct relevance in determining optimal clinical management for these patients. The results for case 1 are illustrated in Table 2. Although factor assays, platelet aggregometry, and nucleotides were all normal, plasma VWF levels were significantly reduced and consistent with low VWF. Because plasma VWF levels are known to vary significantly over time, recent guidelines have recommended repeat testing to ensure consistency in levels prior to assignation of a diagnosis. Importantly, there is limited evidence to guide when repeat testing should best be performed.[11] In our institution, in all patients with plasma VWF levels in the low VWF range, repeat VWF testing is performed a minimum of 3 months after initial sampling. Repeat testing in our index case confirmed that the low VWF levels were a consistent finding (Table 2).

A number of variables may impact significantly upon plasma VWF levels. In particular, it is well described that plasma VWF levels are 25% lower in blood group O individuals compared with non-O individuals.[24,25] In addition, plasma VWF levels have been reported to vary according to the menstrual cycle and can be affected by use of the combined oral contraceptive pill.[26-28] Interestingly, plasma VWF levels also exhibit diurnal rhythm, with peak levels at midday and an amplitude of 22%.[29] Although these factors and others have the potential to influence plasma VWF levels, expert consensus guidelines recommend against the need for timing of samples to menstrual cycle or the use of blood group–specific reference ranges.[9,11]

In terms of assigning a formal diagnosis of low VWF, it is important to note that consensus guidelines differ with respect to their recommended laboratory criteria. The National Heart, Lung, and Blood Institute and the UK Haemophilia Doctors Organization recommend diagnosis for individuals with plasma VWF levels in the range of 30 to 50 IU/dL.[9,11] In contrast, however, the European Group on von Willebrand Disease proposes a plasma VWF threshold level of 30 to 40 IU/dL.[10] Recent data from the Low VWF Ireland Cohort study and the Zimmerman program have shown that there is no significant difference in bleeding for low VWF patients with lowest VWF levels in the range of 30 to 39 IU/dL compared with those with lowest VWF levels in the range of 40 to 50 IU/dL.[7,13] Based upon these cumulative findings, it is our practice to diagnose low VWF for patients with a significant ISTH BAT score who also have ≥2 consistent plasma VWF levels in the range of 30 to 50 IU/dL, taken ≥3 months apart. Our index case clearly satisfies these criteria. In our practice, all newly registered low VWF patients are advised to minimize nonsteroidal anti-inflammatory drug exposure when possible. In addition, patients are provided

Table 2. Hemostatic investigations performed in the investigation of bleeding phenotype for case 1

Test	Results	Repeat testing	Normal reference range
Hemoglobin, g/dL	13.7		11.5-16.4
MCV, fL	95.3		83-98
MCH, pg	30.9		26.7-32.5
Platelets, $\times 10^9$/L	250		140-400
Ferritin, μg/L	8.0		20-300
TSH, mU/L	1.79		0.45-3.5
T3, nmol/L	1.4		1.2-2.5
Free T4, pmol/L	11.3		9-21
Routine coagulation			
APTT, s	34		24-36
PT, s	11.8		9.7-12.8
Fibrinogen, g/L	3.0		2.2-4.3
VWF assays, IU/dL			
VWF:Ag	38	40	50-173
VWF:RCo	36	37	50-156
VWF:CB	40	39	50-150
Coagulation factors, IU/dL			
Factor II	122		72-131
Factor V	131		63-133
Factor VII	107		51-154
Factor X	105		64-150
Factor VIII	69		60-136
Factor IX	119		57-189
Factor XI	87		72-152
Factor XIII	80		73-160
Platelet aggregometry			
Adrenaline, 10 μM	Normal response		
ADP, 2 μM	Normal response		
Ristocetin, 1.25 mg	Normal response		
Ristocetin, 0.5 mg	No response		
Arachidonic acid, 1 μM	Normal response		
Platelet nucleotides, nmol/10^8 platelets			
Platelet ATP	6.1		3.5-6.8
Platelet ADP	3.3		2.1-4.5
Total nucleotides	9.4		5.6-11.3
Ratio	1.8		1.1-2.1

ADP, adenosine diphosphate; APTT, activated partial thromboplastin time; ATP, adenosine triphosphate; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PT, prothrombin time; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

with a standardized letter for their dentist and given emergency contact information in the event of bleeding. Finally, they are informed to contact for a hemostatic management plan should any operations/procedures be required in the future or should they become pregnant.

Management of low VWF for elective major surgery

Case 2

A 26-year-old man with low VWF is scheduled to undergo elective tonsillectomy for recurrent tonsillitis. The patient was diagnosed with low VWF following investigation for recurrent epistaxis. This epistaxis has been problematic since childhood, with frequent nosebleeds lasting for 30 minutes that had responded poorly to previous cauterization. A previous DE was complicated by persistent bleeding that necessitated dental review and suturing. The only abnormality identified on extensive laboratory investigations was persistently reduced plasma VWF levels, with baseline VWF:Ag and VWF:RCo levels consistently in the range of 30 to 40 IU/dL. In view of his significant bleeding phenotype, the patient had previously undergone a trial of 1-desamino-8-D-arginine vasopressin (DDAVP; 0.3 mg/kg, IV). A significant and sustained increase in plasma VWF levels was observed following DDAVP administration (1 hour post-DDAVP: plasma VWF:Ag, 148 IU/dL and VWF:RCo. 150 IU/dL; 4 hours post-DDAVP: VWF:Ag, 97 IU/dL and VWF:RCo, 102 IU/dL).

Discussion of case 2

On the basis of his bleeding history, this patient has an elevated ISTH BAT score of 6. This significant bleeding tendency appears discrepant to the moderate reduction in his plasma VWF levels. Given the prevalence of low VWF levels in the general population, it is perhaps unsurprising that previous studies have described the coincidental occurrence of additional bleeding disorders in some patients with low VWF resulting in a multifactorial bleeding defect. However, using the panel of investigations listed in Table 2, no abnormality other than his low VWF was identified. Interestingly, a number of recent independent studies have confirmed that some patients with low VWF may have significant bleeding phenotypes, even in the absence of any other detectable additional hemostatic abnormalities.[7,13] These observations are in keeping with the original concept proposed by Evan Sadler, wherein the bleeding phenotype observed in patients with low VWF levels was not likely to be attributable solely to the moderate reduction in plasma VWF levels alone. Rather, it seems likely that these patients may have other factors contributing to their bleeding, although definition of these additional modulators using standard laboratory testing may be difficult. Hence, low VWF should be considered an epidemiologic risk factor for bleeding rather than a disease.[16] For example, it should be noted that current routine hemostatic testing cannot exclude other disorders, such as collagen vascular defects or certain platelet function defects (such as those identified on platelet electron microscopy). Critically, therefore, when it comes to defining patient-management plans, personal and family bleeding history are more important than absolute VWF levels. The objective BAT score is useful in this context and undoubtedly serves to facilitate communication between the multidisciplinary health care professionals involved in providing care for these patients. On the basis of his bleeding history and low VWF levels, this patient will require hemostatic cover for his elective tonsillectomy.

Treatment options for patients with low VWF

Treatment options for patients with low VWF and significant bleeding phenotypes include antifibrinolytic agents, such as tranexamic acid or aminocaproic acid, DDAVP, and VWF-containing concentrates. Tranexamic acid has been widely used in the management and prevention of bleeding in VWD.[9] Tranexamic acid can be administered orally (typical dose 15-25 mg/kg, 3 times a day), as a mouthwash (typical dose 10 mL of 5% weight-to-volume ratio solution, 4 times a day), or IV (typical dose 15 mg/kg, 3 times a day).[30,31] Adverse effects associated with use of tranexamic acid include nausea, vomiting, and abdominal pain.[30] In addition, tranexamic acid is generally avoided in patients with significant hematuria (to prevent ureteric clot colic and obstruction).[30] Although concerns regarding possible thromboembolic risk with tranexamic acid therapy have been expressed, recent systematic reviews have failed to demonstrate any significant increased risk.[32-34]

DDAVP is a synthetic analog of vasopressin that stimulates endothelial cell secretion of stored VWF into the plasma.[35] Consequently, DDAVP can be used to transiently increase plasma VWF levels in some patients with VWD.[9] DDAVP is licensed for IV, intranasal, and (in some countries) subcutaneous administration.[36-38] Dosing is route dependent, with 0.3 μg/kg given IV/subcutaneously and 300 μg to adults intranasally. Interestingly lower doses of DDAVP have also been reported to elicit significant plasma VWF responses.[39-41] For patients with type 1 VWD, significant interindividual variability in VWF responses to DDAVP has been reported.[42] However, for a given individual patient, VWF responses to DDAVP administration are typically reproducible over time.[41] These findings likely reflect the different pathogenic mechanisms that can underlie type 1 VWD.[43,44] For example, type 1 VWD patients with *VWF* mutations that interfere with VWF synthesis are unlikely to have significant endothelial cell stores of VWF and, thus, are less likely to respond to DDAVP.[44] In contrast, type 1 VWD can also result from enhanced VWF circulatory clearance (eg, VWF Vicenza R1205H).[45] Plasma VWF levels typically increase significantly in type 1C VWD patients following DDAVP, but the half-life of the secreted VWF is markedly reduced.[45] Given this interindividual variation, a DDAVP trial is usually recommended for patients with VWD.[9,11] In addition to measuring peak VWF responses at 30 to 60 minutes following DDAVP, assays are commonly repeated at later time points (4-6 hours) to confirm the duration of VWF response.[11] Recent data suggest that, in contrast to type 1 VWD, the vast majority of patients with low VWF demonstrate excellent and sustained responses to DDAVP.[13] In the Low VWF Ireland Cohort study, 100% of low VWF patients studied had plasma VWF:Ag and VWF:RCo levels $>$ 50 IU/dL at 1 and 4 hours post-DDAVP. In addition, plasma VWF levels were $>$100 IU/dL in 88% patients at 1 hour and were sustained in 72% patients at 4 hours.[13] On the basis of these findings, we no longer perform routine DDAVP trials in patients with low VWF levels but instead monitor plasma VWF levels over time to confirm adequacy of response at the time of first therapeutic use of DDAVP.

With respect to our index case, he has previously been shown to have an excellent initial and sustained VWF response to DDAVP.

Consequently, for his elective tonsillectomy, we would treat with DDAVP and tranexamic acid. Tranexamic acid (1 g, 3 times a day) would be commenced preoperatively and continued for 7 to 10 days.[46-48] DDAVP (0.3 μg/kg in 100 mL of normal saline infused over 20 minutes) would be administered on the morning of his procedure, with plasma VWF:Ag, VWF:RCo, and FVIII:C levels checked 1 hour post-DDAVP, prior to surgery. Postoperatively, VWF and FVIII levels would be repeated to determine optimal timing for subsequent DDAVP infusions. Although DDAVP treatment can be repeated at 12 to 24–hour intervals, as required, tachyphylaxis with a progressive decrease in response has been reported; thus, plasma VWF levels should be monitored.[49] In terms of adverse effects, DDAVP can cause fluid retention, secondary hyponatremia, and seizures.[36] Fluid intake should be restricted to 1 L for adults in the 24 hours post-DDAVP administration to minimize the risk of dilutional hyponatremia, the rate of which may be higher in adolescents.[11,50] Confirmation of normal serum sodium levels is essential prior to any subsequent doses of DDAVP.[11] Plasma FVIII and VWF levels should be monitored daily and maintained at >50 IU/dL for 5 to 7 days posttonsillectomy.[11] Because the eschar posttonsillectomy may shed at days 7 to 10, there is an increased risk for bleeding during this time period, and we advise continuing tranexamic acid for 7 to 10 days postoperatively. Additional doses of DDAVP should be considered for any bleeding complications that may develop, despite ongoing tranexamic acid therapy.

Given the prevalence of low VWF levels, patients may require management in settings outside of Hemophilia Comprehensive Care Centers where laboratory testing may be delayed. In this setting, our practice is to base treatment on the patient's bleeding history, the bleeding risk associated with the surgical procedure, and plasma VWF response to any previous DDAVP administration. Many patients with low VWF can be managed using a single preoperative dose of DDAVP combined with tranexamic acid (1 g, 3 times a day) for 5 to 7 days postoperatively. If the patient has a very significant bleeding history or develops any postoperative bleeding, despite being on tranexamic acid therapy, we advise repeat DDAVP administration provided that no hyponatremia is present.

For patients with low VWF and significant bleeding histories who are intolerant of DDAVP therapy (eg, who develop significant hyponatremia despite fluid restriction) or for whom DDAVP is contraindicated, a number of commercial plasma-derived VWF-containing concentrates are available. These VWF concentrates differ in several aspects, including source of plasma, purification methodology, viral inactivation steps, and FVIII content (recently reviewed by Lavin and O'Donnell).[51] In addition, a first recombinant VWF concentrate has recently been developed and licensed for use in some countries.[36]

Management of low VWF during pregnancy

Case 3

A 30-year-old woman with a diagnosis of low VWF attends the combined hematology-obstetrics clinic at 20 weeks' gestation in her second pregnancy. She was diagnosed with low VWF 5 years ago, when her ISTH BAT score was calculated as 6 (HMB since menarche, easy bruising, and epistaxis lasting up to 20 minutes requiring consultation). Consistently reduced plasma VWF levels were observed on repeat testing (VWF:Ag, 42 IU/dL; VWF:RCo, 44 IU/dL; VWF:CB, 45 IU/dL). A full bleeding state work-up identified no other hemostatic defects. Subsequent to her diagnosis with low VWF, the patient became pregnant in 2015. Laboratory testing performed during that first pregnancy confirmed that, by the third trimester, her plasma VWF levels had increased significantly (32 weeks' gestation: VWF:Ag, 167 IU/dL; VWF:RCo, 142 IU/dL). Onset of labor was spontaneous, and labor was not prolonged, with normal vaginal delivery of a healthy female infant. No episiotomy was required, and the placenta was delivered intact. Unfortunately, however, she experienced a significant primary postpartum hemorrhage (PPH), with estimated blood loss of 1100 mL, and was treated with tranexamic acid and transfusion. In addition to this personal bleeding history, there is a significant family history of bleeding. Two of her 5 siblings have also been registered with low VWF, and her older sister has an ISTH BAT score of 10.

Discussion of case 3

Normal pregnancy is associated with a progressive increase in VWF, such that plasma levels gradually increase from the first trimester through to term, by which time there is usually a twofold to threefold increase.[52] This pregnancy-related increase means that, by the third trimester, almost all female patients with low VWF have plasma VWF:Ag levels > 50 IU/dL. In fact, in our experience and as observed for our index case during her first pregnancy, most of these women actually achieve term VWF:Ag levels > 100 IU/dL.[21]

Despite the fact that, in most women with low VWF plasma, VWF levels increase into the normal range (50-200 IU/dL), it is important to note that VWF levels remain significantly lower than those observed in normal pregnant women of similar gestation.[21,52] Nevertheless, consensus guidelines recommend that neuraxial anesthesia, vaginal delivery, and caesarean section can proceed without the need for additional hemostatic treatment, provided that plasma VWF levels are maintained >50 IU/dL.[53,54] Plasma VWF levels were repeated in our index case when she reached 34 weeks' gestation in her current pregnancy. Because these demonstrated VWF:Ag, 169 IU/dL and VWF:RCo, 158 IU/dL, no hemostatic therapy was recommended prior to her delivery.

Following delivery, plasma VWF levels gradually decrease, such that baseline levels are typically attained ~3 weeks postpartum.[52,55] Consequently, it is perhaps unsurprising that significantly increased rates of secondary PPH (defined as excessive bleeding between 24 hours and 12 weeks postpartum)[53] have been described in women with low VWF and type 1 VWD (Table 3). For example, in women with VWD, secondary PPH has been reported in up to 33% of cases[21,56,57] (Table 3). Interestingly, despite the pregnancy-related increase in plasma VWF levels, recent studies have also observed a 1.5-fold increased risk of primary PPH (defined as blood loss ≥ 500 mL within 24 hours postpartum) in women with type 1 VWD.[58,59] Significant primary PPH has also been reported in women with low VWF (in all of whom plasma VWF:Ag levels exceeded 50 IU/dL), with 22% requiring transfusion.[21] Together, these findings suggest that higher plasma VWF levels may be required to maintain optimal hemostasis in the peripartum period. This hypothesis is supported by the observation that, even in women with VWD

Table 3. Pregnancy outcomes in patients with partial quantitative VWD (low VWF and type 1 VWD)

Study	Total no. women with VWD (deliveries)	No. with type 1 VWD or low VWF	PPH rates in women with quantitative VWD (unless specified), %	Baseline prepregnant plasma VWF levels, median (range), IU/dL
Ramsahoye et al[56]	13 (24)	n = 7, type 1, 13 deliveries	Primary, 0; secondary, 23.1	VWF:Ag, 8 (5-40); VWF:Act, 7 (3.1-26)
Kadir et al[57]	31	n = 27, type 1, 54 deliveries	Primary, 18.5; secondary, 20	VWF:Ag, 43 (0.5-72); VWF:Act, 40 (0.5-70)
Ragni et al[65]	38	Type 1, n = 38	Overall PPH, 13.1	Mean VWF:Ag, 62
Kouides et al[66]	48	Type 1 VWD, n = 25	Primary, 42 (in all VWD)	No baseline levels provided
Kirtava et al[67]	102	All VWD, subtype unspecified	Overall PPH, 59	No baseline levels provided
James and Jamison[58]	4067	All VWD, subtype unspecified	Overall PPH, 6	No baseline levels provided
De Wee et al[68]	314 (691)	Type 1, n = 242	Overall PPH, 37	Not provided; all patients <30 IU/dL
Chee et al[69]	33 (62)	Type 1, n = 24	Primary, 19.4 (in all VWD)	Not provided; included those <50 IU/dL
Stoof et al[59]	154 (185)	Type 1, n = 49; 56 deliveries	Primary, 37	Median VWF:Act, 50
James et al[52]	32 (35)	Type 1, no treatment required, n = 17	No PPH reported	Mean VWF:Ag, 57; Mean VWF:RCo, 42
Hawke et al[62]	33 (62)	Type 1, 39 deliveries	Primary PPH, 18; secondary PPH, 29 (in all VWD)	No baseline levels provided
Govorov et al[70]	34 (59)	Type 1, n = 21; 39 deliveries	Primary, 46.2; secondary, 10.3	No baseline levels provided
Sood et al[55]	11 (11)	Type 1, n = 11	Primary, 9 (1/11); secondary, 9 (1/11)	Mean VWF:Ag, 41.1; Mean VWF:Act, 34.4
Lavin et al[21]	74 (181)	Low VWF, n = 74; 181 deliveries	Primary, 48.6; secondary, 33.7	VWF:Ag, 49 (33-72); VWF:RCo, 39 (30-54)

Table 4. Clinical scenarios encountered in the management of patients with low VWF

	Alternate clinical scenarios	Clinical assessment	Suggested management strategy
Case 1	22-y-old male with low VWF	Assess personal and family bleeding history	Single dose of DDAVP before DE
	Baseline plasma VWF:Ag, 35 IU/dL; VWF:RCo, 32 IU/dL	Calculate ISTH BAT score	If no previous record of DDAVP response, assess plasma VWF levels at baseline and 1, 2, and 4 h post-DDAVP
	Requires a surgical molar DE	Determine whether the patient has previously been treated for any procedures with tranexamic acid and/or DDAVP	Tranexamic acid, 1 g, 3 times a day for 3-5 d postprocedure
			Contact details in case of bleeding
Case 2	65-y-old with history of low VWF levels	Assess personal and family bleeding history	Treatment plan will be based upon global risk assessment for bleeding and thrombotic potential
	Baseline plasma VWF:Ag, 32 IU/dL; VWF:RCo, 30 IU/dL	Calculate ISTH BAT score	If risk of stroke outweighs bleeding risk, consider introduction of anticoagulation with regular ongoing follow-up at 3 monthly intervals to reassess
	More recent plasma VWF:Ag and VWF:RCo levels now consistently >50 IU/dL	Consider any comorbidities/medications that may contribute to current bleeding risk	Provide contact details in case of bleeding
	Has developed persistent atrial fibrillation	Determine CHA2DS2-VASc score to assess risk of CVA	
Case 3	70-y-old woman with low VWF levels	Assess personal and family bleeding history	If elevated bleeding history, treat with tranexamic acid cover (1 g preoperatively and 1 g, 3 times a day postoperatively for 48-72 h
	Baseline plasma VWF:Ag, 40 IU/dL; VWF:RCO, 44 IU/dL	Calculate ISTH BAT score	Daily review by Coagulation Service to determine when tranexamic acid can be discontinued and LMWH introduced. Thromboembolic Deterrent Stockings.
	More recent plasma VWF levels consistently >70 IU/dL	Consider any comorbidities/medications that may contribute to current bleeding or thrombotic risks	Early mobilization as surgically appropriate
	Requires elective total knee replacement		

CVA, cerebrovascular accident; LMWH, low molecular weight heparin.

treated with VWF concentrate peripartum to maintain plasma VWF levels > 50 IU/dL, up to 33% still experienced a primary PPH.[59] The important clinical question of whether higher VWF dosing regimens at delivery may be more efficacious in reducing PPH rates in women with reduced VWF levels is being addressed in ongoing studies.[60]

The postpartum period is associated with increased fibrinolysis, and recent data from the WOMAN study have highlighted the efficacy of early tranexamic acid administration in the management of primary PPH.[61] Importantly, this therapeutic effect was achieved without any significant increase in thromboembolic events.[61] Similarly, the use of prophylactic tranexamic acid in women with VWD has also been associated with a significant reduction in secondary PPH.[62] On this basis, recent consensus guidelines have suggested that tranexamic acid be considered for use in women with VWD in the postpartum period.[53] With respect to our index case, it is notable that she developed a significant primary PPH following her first delivery, despite having plasma VWF:Ag levels > 100 IU/dL. Consequently, we would recommend prophylaxis with 1 g of tranexamic acid IV to commence at the time of delivery and to continue (1 g, 3 times a day) for 7 days postpartum. Current evidence suggests that, although limited amounts of tranexamic acid are secreted into breast milk, these are too low to impact the infant.[63] Should the patient develop significant bleeding complications despite tranexamic acid prophylaxis, we would consider second-line therapy with DDAVP. DDAVP is minimally excreted in breast milk, and previous experience suggests that it is safe for use during pregnancy and the postpartum period.[36]

In most families with type 1 VWD, the condition is inherited in an autosomal-dominant manner, albeit with variable penetrance.[5,43,64] In contrast, however, the genetic and molecular bases underlying the pathogenesis of low VWF levels remain poorly understood. These provide significant issues in relation to counseling of parents prior to delivery. Critically, several previous studies have demonstrated that, in >50% families, low VWF does not display linkage to the *VWF* gene on chromosome 12.[12] Nevertheless, as illustrated in this case, low VWF levels can be inherited in some families. Further studies are investigating the genetic basis underpinning low VWF. Regarding management of the fetus in this case, the bleeding risk is considered low, and consensus guidelines suggest that no specific precautions are required.[53]

Table 5. Key outstanding questions for future study in low VWF

1. What is the genetic basis underlying the reduction in plasma VWF levels in families with low VWF levels in whom no *VWF* gene sequence variants have been identified?
2. In families with low VWF due to other genetic loci, what is the inheritance pattern, and how does bleeding phenotype relate to low VWF levels?
3. What are the molecular mechanisms underpinning low VWF levels? In particular, what is the relative importance of reduced endothelial cell synthesis/secretion vs enhanced circulatory clearance?
4. In establishing the diagnosis of low VWF, should a specific BAT score be preferred?
5. For patients with low plasma VWF on initial testing, what is the optimal time frame for performing repeat VWF testing to confirm an accurate diagnosis of low VWF?
Conversely, is there a threshold plasma VWF level (even allowing for acute phase–induced transient increases in plasma VWF) above which retesting is not in order?
6. Why is HMB such a common clinical presentation in women with low VWF levels? Does this simply relate to the hemostatic function of VWF or might other emerging biological functions of VWF (eg, regulation of angiogenesis) also be of importance?
7. Are DDAVP trials necessary for patients with low VWF?
8. In managing women with low VWF peripartum, what target plasma VWF levels should be used to reduce the high reported rates of primary and secondary PPH?
9. How should minor and major surgery be managed in patients with low VWF who have a very significant bleeding history? Is correction of the mild reduction in plasma VWF levels adequate to completely revert the bleeding phenotype?
10. Recent data have shown that plasma VWF levels often correct to within the "normal" range (50-150 IU/dL) in patients with low VWF with aging. Does this mean that the bleeding phenotype has been ameliorated, especially in patients with a previously severe bleeding phenotype?

Conclusions

In spite of the population prevalence of low VWF levels, the diagnosis and management of these patients continues to pose significant clinical challenges (Table 4). The diagnosis of low VWF levels should be a clinicopathological one, reliant on both the presence of low VWF levels and a personal history of bleeding. The subsequent clinical management of patients with low VWF should be based primarily upon their personal and family bleeding histories. The challenges in the management of patients with low VWF levels are predominantly attributable to the fact that we have limited understanding of the molecular mechanisms involved in the pathogenesis of low VWF levels. Clinical management of low VWF is further complicated by the fact that these patients commonly display variable bleeding phenotypes. In addition, few previous clinical trials have focused primarily on subjects with low VWF. Additional adequately powered studies are urgently required to address a series of critical basic scientific and clinical questions (Table 5), so that treatment of patients with low VWF can be optimized to enable the development of evidence-based treatment guidelines.

Authorship

Contribution: M.L. and J.S.O. wrote and reviewed the manuscript.

Conflict-of-interest disclosure: M.L. has served on the advisory board for Baxalta and was a member of the speaker's bureau for Shire. J.S.O. has served as a member of the speaker's bureau for Baxter, Bayer, Novo Nordisk, Boehringer Ingelheim, Leo Pharma, and Octapharma; has served on the advisory board for Baxter, Bayer, Octapharma, CSL Behring, Daiichi Sankyo, Boehringer Ingelheim, and Pfizer; and has received research grant funding awards from Baxter, Bayer, Pfizer, and Novo Nordisk.

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Footnote

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