ASH Special Educational Symposium

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Bleeding Disorders in Premenopausal Women: (Another) Public Health Crisis for Hematology?

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Premenopausal women with bleeding disorders represent a major public health problem. Estimates suggest up to 20% of women with menorrhagia have an underlying bleeding disorder (corresponding to a prevalence of 1.5-4 million American women). Von Willebrand disease (VWD) is the most common bleeding disorder among women with menorrhagia, affecting up to 20% of such patients. Besides menorrhagia, important consequences of bleeding disorders in premenopausal women include iron deficiency anemia, miscarriage, postpartum bleeding, uterine bleeding and hysterectomy. These patients face many obstacles in achieving optimum care. Recognition is difficult as women may consider their symptoms "normal" and come to attention only after serious bleeding events. Symptoms of VWD may also overlap with benign conditions, primary providers may not suspect the diagnosis, and convenient hematologic input may be unavailable. Diagnosis is difficult as there is no single definitive test for VWD, and test results are variable, often being affected by extragenic factors, including stress, contraceptives, hormones, and pregnancy. Hemostatic treatment is limited by DDAVP tachyphylaxis, the lack of recombinant VWD concentrates, and the ineffectiveness of hormonal therapy, leading to unnecessary procedures and early hysterectomy. Finally, significant controversy exists regarding classification of type 1 VWD as a disease: given the overlap in symptoms and laboratory assays within the normal population, evaluation for those with VWD might be seen as identification of potential bleeding risk rather than detection of a disease. This symposium seeks to explore these issues in greater detail from the combined perspectives of the obstetrician-gynecologist and the hematologist to promote a better public health approach to this problem.

On behalf of the Committee on Practice (COP) for the American Society of Hematology, the Quality Subcommittee wishes to highlight major public health issues in hematology for our practice community. Last year, the subject of anemia in the elderly (a condition that affects 3 million Americans) was reviewed. This year, the COP wishes to examine a second important public health issue in hematology, specifically, that of bleeding disorders in premenopausal women. It is estimated that these disorders affect a like number of our citizens and, like anemia in the elderly, frequently go unrecognized and/or untreated. As patients with these disorders most commonly present initially to our colleagues in obstetrics and gynecology, we will examine this problem from the perspectives of the obstetrician/gynecologist, the hematologist, and from society as a whole.

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Overview

Menorrhagia represents a major public health problem in women. As many as 10-15% of women experience menorrhagia during their lifetime. These patients account for 15% of all referrals to gynecologists and over 300,000 hysterectomies annually.[1] The prevalence of bleeding disorders among women with menorrhagia is high; up to 20% (which equates to approximately 2-3 million American women) have an underlying bleeding disorder, most commonly von Willebrand disease (VWD).[2] Conversely, menorrhagia is the most common presenting symptom among women with VWD, occurring in over 90% of patients.[3] The morbidity of

this condition is also high, and includes a variety of medical complications, lost work time, lifestyle and psychological disruption, poor quality of life and increased health costs.[4] Although quantitatively defined as bleeding exceeding 80 cc per month based on its association with anemia,[5] menorrhagia is generally a subjective diagnosis.

Despite their high prevalence in premenopausal women, bleeding disorders (and particularly VWD) often remain undiagnosed, and particularly so unless significant iron deficiency anemia, postoperative bleeding and/or transfusion occurs. Why is this so? Major reasons include 1) the failure to recognize or even consider a diagnosis of a bleeding disorder either by patients or providers; 2) the limitation of available diagnostic tests, which are complex and frequently inexact, and 3) the lack of available therapeutic agents with which to treat such patients chronically. Diagnosing VWD is especially difficult: although it is caused by deficient or defective von Willebrand factor (VWF), there is no single definitive test that confirms the diagnosis. Laboratory assays are difficult to perform and influenced by extragenic factors, sampling and storage conditions. The genetics are complex, and the presence of low VWF levels does not correlate with symptoms, suggesting that VWF may be a marker for bleeding risk rather than a diagnostic test. The link between specific molecular defects leading to VWD and the natural history of the disease is poorly defined, and despite ongoing clinical and biochemical studies to improve our understanding of the clinical aspects of VWD, treatment is suboptimal, with invasive, inconvenient, short-duration protein-based or high-cost plasma-derived products.

Despite these limitations, a number of exciting new developments are on the horizon, including 1) a new diagnostic clinical scoring system for VWD based on bleeding symptoms; 2) genotype-phenotype studies in VWD kindreds to determine markers for bleeding risk; 3) standardization of VWD assays among laboratories; and 4) clinical trials of new, less invasive recombinant agents.

Based on the magnitude of health problems associated with menorrhagia in women with bleeding disorders, the National Heart, Lung & Blood Institute (NHLBI) convened two separate panels in the spring of 2004[1]: a Consensus Panel of 10 experts in hematology, family medicine, obstetrics and gynecology, pediatrics, laboratory medicine, and basic science, to develop guidelines for VWD diagnosis, treatment, and management,[6] and 2) a Working Group of 15 scientific experts in hematology, obstetrics and gynecology to identify key research objectives to reduce VWD morbidity.[7] This review emphasizes recommendations of these expert panels.

Table 1. Previously undiagnosed bleeding disorders in patients with menorrhagia.[8-14]

Bleeding Disorder	Prevalence in Women with Menorrhagia
Von Willebrand disease	5-20%
Platelet dysfunction	< 1-47%
Factor XI deficiency	< 1-4.3 %
Hemophilia carriage	< 1-3.5%
Rare factor deficiencies	< 1%

Bleeding Disorders in Premenopausal Women—The View of the Obstetrician-Gynecologist

~Andra H. James

Significance and magnitude of the problem

Women bleed. They bleed with menstruation and they bleed with childbirth or miscarriage. Due to these bleeding challenges, premenopausal women (females in their childbearing years) are more likely to manifest a bleeding disorder than premenarchal females, postmenopausal females, or men. The prevalence of undiagnosed bleeding disorders among women with menorrhagia is high, with estimates ranging anywhere from 5-20%[8-14] (**Table 1**). Higher estimates have been reported for platelet dysfunction, but these were based on nonspecific tests such as platelet aggregometry.[15]

As can be seen from **Table 1**, the most common inherited bleeding disorder in women is VWD although it represents only about one-half of all bleeding disorders among women. The diagnosis of VWD is based on a personal bleeding history, a positive family history and a low VWF level. Estimates of the prevalence of VWD among females with menorrhagia are as high as 20%. This is in contrast to estimates of the prevalence of VWD in the general population, which depend on the population studied and the definition of the disease used. Estimates of VWD prevalence based on the number of individuals registered in hemophilia treatment centers range from 0.002% to 0.01% of the population.[16] However, estimates based on identification of individuals with classic criteria for the diagnosis of VWD (i.e., bleeding symptoms, a positive family history and a low VWF level) are much higher, ranging from 0.6% to 1.3% of the population.[17,18] While few individuals have severe symptoms, many with mild symptoms are potentially affected. Also, while both women and men should be seen as "at risk" for a bleeding disorder from a positive family history or low VWF level, women are more likely to have a personal bleeding history and thus more likely to be diagnosed with VWD.[19] In fact, in Erik von Willebrand's original paper published in 1926, he stated that the hereditary hemorrhagic condition he described as "hereditary pseudohemophilia" appeared to affect women twice as often as men.[20] Thus, the presence of abnormal bleeding in a premenopausal female should markedly increase clinical suspicion that a bleeding disorder exists.

Clinical presentation

The most common bleeding symptom among women with bleeding disorders, at least among women with VWD, is menorrhagia. Menorrhagia is defined as heavy, regular menstrual bleeding as opposed to metrorrhagia, which is defined as irregular menstrual bleeding. In a survey con-

ducted by the United States Centers for Disease Control and Prevention (CDC), 84% of women with VWD reported menorrhagia, the highest prevalence for any bleeding symptom[21] (**Table 2**). Menorrhagia is commonly reported in other bleeding disorders as well, including hemophilia carriers, women with afibrinogenemia, combined factors V and VIII deficiency, factors XI and XIII deficiency, Bernard-Soulier syndrome and Glanzmann thrombasthenia.

Women with bleeding disorders may experience even heavier menstrual bleeding in cycles in which ovulation does not occur. During a normal cycle, the endometrium, or lining of the uterus, is first exposed to estrogen, then a combination of both estrogen and progesterone, and finally, to falling levels of estrogen and progesterone. In the absence of ovulation (anovulation), a corpus luteum, which is necessary for the production of progesterone, does not form. In a female of reproductive age, with anovulation, estrogen continues to be produced and the endometrium continues to proliferate, but without the secretory changes induced by progesterone. Eventually, growth becomes unstable and the endometrium begins to bleed.[22] Unlike the synchronized shedding of the endometrium that occurs in a normal cycle, the bleeding may be irregular and prolonged. Anovulation is more likely to occur in adolescence and during the premenopausal years. Not surprisingly, in women with VWD, menorrhagia has been reported to be most severe during the first few years after menarche,[23] but may increase in severity again toward the end of the childbearing years.[24]

Complications of bleeding disorders in premenopausal women

Although menorrhagia may be the most common manifestation of a bleeding disorder in premenopausal women, it is far from the only one. Women with bleeding disorders are vulnerable to chronic anemia from iron deficiency,[25] endometriosis,[26] bleeding from benign pathology such as fibroids, endometrial hyperplasia and polyps, and hemorrhagic ovarian cysts.[27] Hemorrhagic cysts are particularly suggestive of a bleeding disorder. Women with bleeding disorders are also at risk for a variety of obstetrical complications, including miscarriage[26] and obstetrical bleeding, especially secondary or delayed postpartum bleeding.[27] Vaginal or vulvar hematomas, while extremely rare in the general population, are not uncommon in patients with bleeding disorders and their detection should immediately trigger pursuit of such a diagnosis.[27]

However, most manifestations of bleeding in women are not unique to women with bleeding disorders; they are simply more common and severe. In particular, both the risk of life-threatening hemorrhage and the likelihood of hysterectomy appear to be greater. With respect to the latter, women with bleeding disorders also undergo hysterectomy at an earlier age.[26] Premenopausal women with bleeding disorders can, of course, also display the full range of bleeding complications displayed by their male counterparts.

Barriers to hematologic referral

Why are bleeding disorders in women so difficult to recognize, and in particular, why are hematologists so infrequently consulted for this problem? A variety of reasons exists. First, from the patient's point of view, it is difficult to distinguish "normal" from pathological bleeding. In studies comparing women with bleeding disorders to those without, even women without bleeding disorders report an incidence of menorrhagia ranging from 23-69%.[23,26]

Second, from the obstetrician-gynecologist's point of view, a certain amount of bleeding is normal with menstruation, childbirth and miscarriage, and there is a wide variation in the amount of bleeding experienced in these situations among normal individuals. Even an abnormally large amount of bleeding is usually not due to a disorder of hemostasis. For example, most abnormal bleeding in menstruation is explained by anovulation or by an anatomic problem. Most abnormal bleeding with miscarriage is due to retained tissue, and most abnormal bleeding after childbirth is due to failure of the uterus to contract.

Third, as previously stated, there is a spectrum of severity of bleeding among premenopausal patients with bleeding disorders.[28] Previously undiagnosed women with a bleeding disorder who present to an obstetrician-gynecologist may be far less symptomatic than those that present themselves to a hematologist or a hemophilia referral center. Failure to diagnose a patient with a mild disorder may be of little consequence.[29] Even surgery may pose a low risk. There are almost no data to allow estimation of the degree to which VWD increases the risk of bleeding complications at surgery in women with menorrhagia.[30] In a study of women with menorrhagia, among 17 individuals who were found to have previously unreported VWD, none reported a history of postoperative bleeding, and the rate of postpartum bleeding was the same as in controls.[10]

Fourth, most reproductive tract bleeding can be managed by the obstetrician-gynecologist using hormonal or surgical therapy. Combined oral contraceptives,[31] depot

Table 2. Bleeding symptoms in women with von Willebrand disease.[21]

Symptom	Number Reporting	Mean Age at Onset	Percentage of Those Reporting	Percentage Transfused
Bruising	36	7	48	0
Nosebleeds	33	7	44	0
Bleeding after injury	25	11	33	11
Menorrhagia	63	13	84	18
Dental bleeding	38	16	51	36
Postoperative bleeding	36	17	48	12
Postpartum hemorrhage	24	24	32	25

medroxyprogesterone acetate injections,[32] and the levonogestrel intrauterine device[33] reduce menstrual blood loss. After childbearing is complete, other options available include ablation and hysterectomy.

Given the above, perhaps coupled with limited knowledge and experience with hemostatic disorders, obstetrician-gynecologists and other practitioners who see women with reproductive tract bleeding, often fail to consider a bleeding disorder as a contributing factor to symptomatology. In a survey of obstetrician-gynecologists, only 4% responded that they would consider VWD as an explanation for menorrhagia. (Previous guidelines for the management of VWD have been rescinded due to lack of supporting evidence.[34]) In one study in VWD, the delay in onset of bleeding symptoms until diagnosis was an average of 4 years;[5] in another, 16 years.[21] Women with mild as well as those with severe significant bleeding disorders, thus, are deprived of optimal management, including hemostatic therapies.

Finally, obstetrician-gynecologists may well experience a dearth of ready access to the community of hematologists. There is a recognized shortage of hematologists with expertise in hemostasis and thrombosis.[35] In some regions of the country, it may not even be known who the appropriate hematology referral contact is, yet there are situations that absolutely require hematology expertise:

- evaluation of a patient with a suspected bleeding disorder
- laboratory diagnosis of a bleeding disorder
- evaluation of family members of premenopausal women with bleeding disorders
- management of reproductive tract bleeding in women who fail to respond to hormonal therapy
- prescription and monitoring of hemostatic agents for prophylaxis and treatment of bleeding disorders

Bleeding Disorders in Premenopausal Women—The View of the Hematologist

~Margaret V. Ragni

Epidemiology

As many as 20% of women with menorrhagia have an underlying bleeding disorder, of which VWD is the most common. The disease was described by Eric von Willebrand in 1926 in a 5-year-old girl from a large kindred in the Åland Islands, who subsequently died from severe menorrhagia.[28] Type 1 VWD, accounting for 70% of diagnosed individuals, is an autosomal dominant disorder caused by a partial quantitative deficiency of von Willebrand factor (VWF), a multimeric plasma glycoprotein that mediates platelet adhesion to damaged vascular endothelium following injury and serves as a carrier for factor VIII. The bleeding in VWD is primarily mucosal, including epistaxis, easy bruising, gastrointestinal bleeding, oropharyngeal bleeding, and prolonged bleeding after trauma and surgery. In women with VWD, menorrhagia is the most common symptom, occurring in up to 93% of patients.[5] Menorrhagia in VWD patients typically presents at menarche,[5] in contrast to other causes of menorrhagia, e.g., endometriosis, uterine cancer, polyps, and hypothyroidism, which tend to present later in life. Yet, from the perspective of the consulting hematologist, a diagnosis of VWD diagnosis is often not considered until *after* invasive testing is unrevealing or postprocedure bleeding occurs.[5] In clinical practice, menorrhagia is a subjective diagnosis and even in affected families may be considered "normal" and VWD overlooked. VWF levels do not correlate with bleeding symptoms and overlap those in healthy individuals.[29] Thus, failure to diagnose VWD or other bleeding disorder in women with menorrhagia constitutes a major public health problem.

Diagnosis and evaluation

Bleeding during the menstrual cycle is regulated by normal hemostatic mechanisms. Vessel injury is precipitated by the monthly sloughing of the vascular, outer layer of the lining of the uterus or endometrium, leading to vasoconstriction of endometrial vessels, platelet plug formation (primary hemostasis), activation of coagulation, subsequent fibrin clot formation (secondary hemostasis) and gradual cessation of bleeding. When VWF is reduced as in type 1 VWD, platelet plug formation is delayed and defective, and primary hemostasis fails, leading to clinical bleeding. Although VWD is the most common inherited bleeding disorder underlying menorrhagia, other disorders of primary or secondary hemostasis or of the vascular wall, congenital or acquired, may underlie menorrhagia.[36] Thus, women with menorrhagia should be screened for defects in primary or secondary hemostasis or vessel wall abnormalities (**Table 3**).

Disorders of primary hemostasis include congenital diseases, e.g., Bernard-Soulier syndrome, Glanzmann thrombasthenia, storage pool disease, congenital thrombocytopenias, and disorders of platelet dysfunction; and acquired disease, i.e., drug-induced thrombocytopenia or platelet dysfunction, and systemic diseases with thrombocytopenia or platelet dysfunction, such as renal or hepatic disease. Menorrhagia is rare in the latter disorders, unless another defect exists, for example, use of aspirin (ASA) or nonsteroidal anti-inflammatory agents (NSAIDs).

Disorders of secondary hemostasis include congenital diseases, e.g., hemophilia A, B carriers, factor XI deficiency, other factor deficiencies; and acquired diseases, e.g., anti-VIII inhibitors, Vitamin K deficiency, liver disease, and disseminated intravascular coagulation. Menorrhagia is a recognized symptom in women with congenital factor I, II, V, VII, X, and XI deficiencies, although the latter disorders are rare, < 1 in 500,000, but has not been reported in women with factor XII, prekallikrein, or high-molecular-weight kininogen deficiency, as these disorders are not associated with clinical bleeding.

Congenital disorders of the vessel wall including hereditary hemorrhagic telangiectasia and Ehlers-Danlos syndrome may have clinical menorrhagia, while acquired disor-

Table 3. Women with bleeding disorders: differential diagnosis.[45]

	Coagulation Disorders	Platelet Disorders	Vessel Wall Disorders
Congenital			
	Hemophilia A, B carrier	von Willebrand disease	Hereditary hemorrhagic telangiectasia
	Factor XI deficiency	Bernard-Soulier syndrome	Ehlers-Danlos syndrome
	Other factor deficiencies	Glanzmann thromboasthenia	
		Storage pool disease	
Acquired			
	Acquired anti-VIII inhibitor	ITP	Physical: valsalva, weight-lifting
	Vitamin K deficiency	TTP	Infection: bacterial, viral, rickettsial
	Liver disease	Drug: ASA, NSAIDs, antibiotics, chemotherapy	Drug: heparin necrosis coumadin necrosis
	DIC	Collagen diseases: SLE	Dysproteinemias
	Drug: coumadin, heparin, antibiotics	Chronic renal disease	Cutaneous vasculitis
		Leukemias	
		Myeloproliferative disorders	

Clinical Bleeding History

Components of a Clinical Bleeding History

Age at first bleeding symptoms
Frequency, severity
Requirement for transfusion
Spontaneous vs. traumatic bleed
Postoperative bleeding
Family members affected, sex-linked
Medication history

Types of Bleeding

1. Mucosal bleeding
   Defect: Platelet plug formation or "primary hemostasis"
   Symptoms: Menorrhagia, epistaxis, bruising, postoperative, dental, gastro-intestinal, genito-urinary bleeding
2. Body cavity bleeding
   Defect: Fibrin clot formation or "secondary hemostasis"
   Symptoms: Hemarthroses, hematomas, postoperative, retroperitoneal, central nervous system bleeding
3. Petechiae, ecchymoses, purpura
   Defect: Vessel wall abnormality
   Symptoms: Telangiectasia, gravity-dependent lesions, palpable vs. nonpalpable

Adapted from reference [45]
Abbreviations: ITP, immune thrombocytopenic purpura; TTP, thrombotic thrombocytopenic purpura; ASA, aspirin; NSAIDS, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; DIC, disseminated intravascular coagulation

ders of the vessel wall, e.g., vasculitis, dysproteinemias, infections, or drug-induced vascular necrosis, may be associated with purpura, but not typically with menorrhagia.

Genetics

The VWF gene is located on chromosome 12, and the VWF mRNA encodes for the large VWF polypeptide, which is composed of four domains linked by disulfide bonds and containing receptors for platelet glycoproteins Ib/IIa and IIb/IIIa, heparin, collagen, and factor VIII. Because type 1 VWD is autosomal dominant with variable penetrance, bleeding tendency even within families may vary widely, unrelated to VWF levels. Studies in twins have determined that up to 60% of the variation in VWF levels is inherited, 30% of which is due to ABO blood type,[37] resulting in 25-35% lower VWF levels in blood group O.[38] Genetic defects have been identified in more severe forms of type 1 VWD, primarily single amino acid substitutions in the D3 domain, resulting in defective VWF secretion or clearance.[39,40] Because the multimeric structure is normal, mutations are suspected in the promoter region or in genes outside the VWF gene, as demonstrated in the type 1 VWD mouse model. As defects are identified in ongoing US and European phenotype-genotype studies, the database of VWF mutations set up by International Society on Haemostasis and Thrombosis (http://www.shef.ac.uk/vwf/index/html) will expand, the classification system will be revised, and it is anticipated that more precise diagnostic tests will be developed.

Clinical history

Deficiency of VWF may lead to clinical bleeding, but not all affected patients bleed, and there is overlap with bleeding reported in normal healthy individuals (**Table 3**). The bleeding is primarily mucosal, may not occur consistently, and may be worsened by medications, such as aspirin or NSAIDs. Despite the variability, studies have shown that if a bleeding history were taken prior to surgery among women with menorrhagia, two-thirds of postoperative bleeding might be avoided.[5] Clinical evaluation of an individual suspected of having an underlying bleeding disorder should include a history, physical examination, and laboratory screening tests (**Table 4**). The clinical history should include a personal bleeding history, a family history of bleed-

Table 4. Laboratory diagnosis: women with bleeding disorders.[45]

I. Screening Laboratory Studies:

Hematologic tests:	CBC, differential, platelet count
Endocrinologic tests:	Prolactin, FSH, progesterone (mid-cycle)
Liver function tests:	SGOT, SGPT, alkaline phosphatase, bilirubin
Kidney function tests:	BUN, creatinine, urinalysis
Gynecologic tests:	Pelvic ultrasound

II. Screening Coagulation Laboratory Studies:

Coagulation Pathway	Coagulation Abnormality	Congenital Deficiency	Acquired Coagulopathy
Intrinsic Pathway (LAC)	Prolonged APTT	FXI, XII, PK HMW-K FVIII, IX FVIII carrier FIX carrier von Willebrand disease	Lupus anticoagulant Specific anticoagulants Anti-VIII Anti-V Heparin Acquired von Willebrand disease
Extrinsic Pathway	Prolonged PT	FVII	Vitamin K Deficiency
Common Pathway	Prolonged PT, APTT	FI, II, V, X	Vitamin K Deficiency Liver Disease, DIC

III. Screening Platelet Function Studies:

Platelet Plug Pathway	Platelet functional Defect	Congenital Platelet Defect	Acquired Platelet Defect
Platelet Adhesion	Platelet adhesion Ristocetin agglutination	Bernard-Soulier syndrome	Immune thrombocytopenic purpura Myeloproliferative disorders
Platelet Aggregation	Aggregation with epi, ADP collagen thrombin	Glanzmann thrombasthenia	Cardiopulmonary bypass Chronic renal disease Heparin
Platelet Secretion	ATP:ADP ratio	Storage pool disease	
von Willebrand Ag	vW:Ag: ELISA Laurell immunoassay	von Willebrand disease	Acquired von Willebrand disease
vWF Activity	FVIII:C, RCoF:VIII Multimers (SDS PAGE) Collagen binding assay		
Vessel-platelet interaction	Closure time/bleeding time	All above disorders	Aspirin, NSAIDs, antibiotics Platelet inhibitory drugs, ETOH

ing, and history of medications. The bleeding history should include the site, severity, and frequency of bleeding, whether it is spontaneous, mucosal, involves mucosa of the gastrointestinal, genitourinary, or oral cavity, nares, dental tissue, or respiratory tract. Such symptoms as epistaxis lasting 10 minutes, bruising without trauma, prolonged bleeding after dental work, or heavy postoperative bleeding are highly suggestive of a bleeding disorder.[41,42] Questions should also determine if there is bruising with minimal trauma or prolonged bleeding following surgery or procedures, medical or dental. If there is a history of menorrhagia, the number of pads or tampons per day, duration, and presence of anemia or iron replacement should be determined. Of these, the three best predictors of abnormal menstrual blood flow[43] include: 1) clots greater than 1" in diameter, 2) changing pads more frequently than hourly, and 3) a low ferritin. A history of transfusions, postpartum bleeding, and other medical conditions including thyroid, liver, kidney or bone marrow disorders should be determined. The family history should establish if bleeding occurs in males and/or females and if symptoms are variable in family members. A medication history should determine use of aspirin, NSAIDs, antiplatelet or anticoagulant drugs, and hormones.

Physical examination

The exam should evaluate for mucosal bleeding, bruising, petechiae, purpura, and oropharyngeal bleeding, which typify defects in primary hemostasis. Hematomas or hemarthroses suggest a defect in secondary hemostasis, while dermal or mucosal telangiectasias in the oral or nasal mucosa suggest a vascular wall abnormality. The size, location, and distribution of these bleeding signs should be determined, yet the absence of signs or symptoms of bleeding does not exclude a diagnosis of a bleeding disorder, nor does their presence confirm a diagnosis of a bleeding disorder.

Laboratory evaluation

Testing for VWD is complex, and should include FVIII, VWF:RCo, VWF:Ag, platelet function analyzer (PFA-100), multimers, and platelet ristocetin aggregation (**Table 5**). In

Table 5. Treatment of women with bleeding disorders.[45]

Agent	Dose	Disease Indication	Level*	Mechanism	Side Effects
Desmopressin (DDAVP)	0.3 μg/kg IV	Type 1 vWD Hemophilia A carrier Platelet dysfunction	**(A)**	Releases vWF from endothelial cells by binding to ADH	Flushing, headache, tachycardia, hyponatremia, volume overload, tachyphylaxis
Stimate (Intranasal) (1.5 mg/mL)	150 μg/nostril < 50 kg, one nostril ≥ 50 kg, both nostrils		**(A)**	V2 receptor and activating CAMP	
von Willebrand factor concentrate	40 U/kg, then 25 U/kg q 12-24 h	Type II, III vWD Type 1 unresponsive to DDAVP	**(A)**	Replaces vWF	Allergic reaction, hepatitis, transmissible agent
Factor VIII concentrate (Recombinant)	50 U/kg, then 25 U/kg q 8-12 h	Factor VIII deficiency, severe or moderate Acquired vWD	**(A)**	Replaces factor VIII	Allergic reaction
Factor IX concentrate (Recombinant)	75 U/kg, then 38 U/kg q 12-24 h	Factor IX deficiency Hemophilia B carrier	**(A)**	Replaces factor IX	Allergic reaction
Plasma Retested plasma	5 units = 20% level or 10 mL/kg	Factor II, V, XI deficiency Liver disease Vitamin K deficiency DIC, TTP Marrow failure (malignancy, chemotherapy)	**(A)** **(C)**	Replaces factors	Fever, chills, hepatitis, transmissible agent hepatitis, HIV
Cryoprecipitate	6 bags = 1200 mg fibrinogen	Factor I deficiency Dysfibrinogenemia Factor XIII deficiency Uremic bleeding, DIC	**(C)**	Replaces fibrinogen Replaces factor XIII	Fever, chills transmissible agent hepatitis, HIV
Factor VIIa (Recombinant)	90 μg/kg q 2-3 h 20 μg/kg q 6-8 h	Factor VIII inhibitor Factor VII deficiency Glanzmann thrombasthenia	**(A)** **(A)**	Activates tissue factor Replaces factors VII, IX	Thrombosis
Autoplex, FEIBA	75-100 U/kg, then 50 U/kg q 6-8 h	Factor VIII inhibitor	**(A)**	Replaces factor IX Activates tissue factor	Thrombosis, HIV, hepatitis, inhibitor transmissible agent
Platelet transfusion	1 unit/10 kg (to 60 kg)	Thrombocytopenia Bernard-Soulier syndrome Glanzmann thrombasthenia ASA platelet defect Platelet-type vWD DIC	**(A)**	Replaces platelets, restores platelet function	Fever, allergic reactions
Amicar (epsilon amino caprioc acid)	50 mg/kg q 6-8 h	Congenital bleeding disorder	**(A)**	Prevents lysis of clots by inhibiting plasminogen binding to fibrin	Nausea, vomiting, kidney sludge, stone
Tranexamic acid	4 g/day (15 mg/kg)	vWD Hemophilia A, B carrier Factor deficiencies	**(C)**	Prevents lysis of clots by inhibiting plasminogen binding to fibrin	Nausea, vomiting, diarrhea, hypotension
Estrogens	Mid-dose OCP	vWD Hemophilia A,B carrier Factor deficiencies	**(B,C)**	Increases factor levels Endometrial changes	Nausea, headache, thrombosis, cardiovascular risk
Hepatitis A Vaccine Hepatitis B Vaccine		Congenital bleeding disorder	**(A)** **(A)**	Protects from hepatitis A, B	Soreness at site, nonspecific symptoms

* Level of Evidence: **A** indicates that the recommendation is based on clinical trial data; **B** indicates the recommendation is based on laboratory data; and **C** indicates the recommendation is based on opinion of experienced clinicians. It should be noted that the level of recommendation is based on general bleeding symptoms and not on menorrhagia.
Abbreviations: vWD, von Willebrand disease; vWF, von Willebrand factor; ASA, aspirin; OCP, oral contraceptive; DIC, disseminated intravascular coagulation

type 1 VWD, the VWF:Ag and VWF:RCo are generally in a 1:1 ratio, and the FVIII and VWF:Ag (or VWF:RCo) are in a 2:1 ratio. Multimers, measured by sodium dodecyl sulfate agarose electropheresis, are qualitatively normal, and may be decreased. Platelet function testing by PFA-100, although nonspecific, may suggest VWD, platelet disorders, or platelet inhibitory drugs.[44] Samples for VWD testing should be drawn fasting into 3.2% citrate, frozen at –40°C, and, after thawing at 37°C, tested at room temperature. The optimal time to test is the first 3 days of the menstrual cycle, when estrogen is lowest; ideally, testing should be repeated three times and delayed at least 6-8 weeks following delivery or cessation of estrogen.

To evaluate for other bleeding disorders,[45] a complete blood count, hemoglobin, hematocrit, platelet count, MCV, prothrombin time (PT), and activated partial thromboplastin time (APTT) mix, fibrinogen, and thrombin time should be obtained (**Table 4**). Prolongation of the PT indicates a

Table 6. The bleeding score for von Willebrand disease.[46,47]

Symptoms	Assigned Score	Number Events
Epistaxis	0	no or trivial
	1	present
	2	packing/cauterization
	3	transfusion/replacement
Cutaneous symptoms	0	no or trivial
	1	petechiae/bruises
	2	hematomas
	3	medical consultation
Minor wounds	0	no or trivial
	1	present (1-5 per year)
	2	medical attention
	3	surgical/blood transfusion
Oral cavity bleeding	0	no or trivial
	1	present
	2	medical attention
	3	surgical/blood transfusion
Gastrointestinal bleeding	0	no or trivial
	1	present
	2	medical attention
	3	surgical/blood transfusion
Postpartum hemorrhage	0	no or trivial
	1	present/medical attention/iron therapy
	2	blood transfusion/ D&C/ suturing
	3	hysterectomy
Muscle hematomas or hemarthrosis	0	no or trivial
	1	present
	2	medical attention
	3	transfusion/intervention/replacement rx
Tooth extraction (most severe episode)	0	no or trivial
	1	present
	2	suturing/ packing
	3	transfusion
Surgery (most severe episode)	0	no or trivial
	1	present
	2	suturing/resurgery
	3	transfusion
Menorrhagia	0	no or trivial
	1	present
	2	consultation/pill use/ iron therapy
	3	transfusion/ hysterectomy/ D&C/ replacement rx

deficiency in the extrinsic pathway, while prolongation of APTT indicates a deficiency in the intrinsic pathway, i.e., factor XII, XI, prekallikrein (PK), high-molecular-weight kininogen, VIII, IX, FVIII carrier, FIX carrier, and VWD. In up to 50% of those with VWD, the APTT is normal, which should not discourage VWD testing. Prolongation of both PT and APTT suggests a defect in the common pathway, including deficiency of factor X, V, II, or I, or acquired disorders, e.g., Vitamin K deficiency or liver disease. A prolonged APTT should be further evaluated by a mixing study to distinguish factor deficiency from clotting factor inhibition. A failure to correct the APTT upon mixing with normal plasma should be further pursued by a Bethesda assay to evaluate for an anti-VIII antibody or other inhibitor, a thrombin time to evaluate the possibility of heparin contamination and the hexagonal lipid assay to assess the potential presence of a lupus anticoagulant.

Tests for disorders of platelet function include platelet adhesion, aggregation, platelet count, and platelet function analyzer (PFA-100). Defects in platelet adhesion may suggest the congenital disorder Bernard-Soulier syndrome, or acquired platelet defects in ITP or myeloproliferative disorders. Defects in platelet aggregation suggest the congenital disorder Glanzmann thrombasthenia or acquired disorders, such as renal disease or cardiopulmonary bypass.

An exciting development in diagnosis has been the introduction of a quantitative scoring system[43] that rates bleeding symptom severity from 0 to 3 (**Table 6**). The derived "bleeding score" has 96.8% specificity and 69.1% sensitivity for type 1 VWD.[46] In a validation of the system in 177 members of 144 kindreds (http://www.shef.ac.uk/euvwd/bleed_score.htm), the "score" was found to correlate directly with surgical/procedural bleeding, and indirectly with VWF:RCo, VWF:Ag, and FVIII levels.[47] This "score" thus appears to be a potentially useful quantitative predictor of bleeding risk. Further studies will be needed to confirm these findings. However, it should be recognized that, given the overlap of symptoms and laboratory findings with normal controls, and in the absence of a single definitive diagnostic test, the diagnosis of VWD remains difficult and controversial. Further studies are clearly needed to improve VWD diagnosis.

Management—general considerations

The consulting hematologist plays a pivotal role in the care of women with bleeding disorders (**Table 7**). In addition to taking a careful and complete history and obtaining coagulation testing, the hematologist should discuss with the affected woman a treatment plan for future bleeding problems and testing of family members, and communicate with the primary care provider. DDAVP testing should be performed to determine response for future surgeries, taking care to avoid testing within three weeks of anticipated surgery, to avoid depletion of VWF stores and subclinical DDAVP response. Hepatitis A and B vaccination, if not previously given, should be administered, as per current US Public Health guidelines for individuals with bleeding disorders. The potential risk for increased bleeding associated with the use of aspirin and NSAIDs in women with bleeding disorders should be discussed. The hematologist should also assure that menorrhagia or unexplained symptoms in a woman with a bleeding disorder are taken seriously, evaluated and treated in a timely fashion, avoiding unnecessary procedures. If surgery is planned, the treatment plan should be made available to surgical and anesthesia staff. In preg-

Table 7. Problems in diagnosis of von WIllebrand disease.

Problems in clinical assessment:

1) Bleeding symptoms do not correlate with laboratory assays
2) Increase in VWF levels with hormones or pregnancy may mask VWD diagnosis
3) There is no precise definition for menorrhagia, the most common symptom in VWD
4) Bleeding symptoms may be atypical and lack specificity for VWD
5) Bleeding symptoms overlap with those in healthy individuals

Problems in laboratory testing:

1) There is no single diagnostic test for VWD
2) VWD assays are difficult to perform, may vary over time, and lack reproducibility
3) There is no laboratory standardization for VWD testing
4) VWF levels do not correlate with genetic defects or bleeding symptoms
5) VWF levels are not specific for VWD and overlap with levels in normal individuals
6) Traumatic sample procurement and poor sample handling interfere with VWD assays

Table 8. How I treat women with bleeding disorders.

Management: General Considerations

1) Take a careful history, perform a physical exam, and obtain laboratory tests
2) Formulate a treatment plan for current, future bleeding problems
3) Individualize and optimize menorrhagia treatment plan with help of gynecologist
4) Test family members
5) Perform DDAVP testing to establish response
6) Vaccinate with hepatitis A, B vaccines, if not previously vaccinated
7) Review bleeding risks associated with aspirin, NSAIDs, other analgesics
8) Review perioperative recommendations with patient and medical team
9) Review potential risks of delayed postpartum and postsurgical bleeding
10) Assist medical team in evaluation of symptoms, and patient in navigation of medical system

Treatment: Hemostatic Agents

1) Consider mid-dose estrogens for initial treatment of menorrhagia
2) Use DDAVP as first-line therapy for VWD—tachyphylaxis, inconvenience limitations
3) Use VWF-containing concentrates in those failing DDAVP or requiring longer treatment
4) Consider antifibrinolytic agents as adjuncts to estrogen or DDAVP for bleeding
5) Avoid cryoprecipitate because of potential transmissible agent risk
6) Avoid heparin, aspirin, NSAIDs, and platelet inhibitory agents
7) Evaluate for iron deficiency when there is menorrhagia or prolonged post-procedure bleeding
8) Evaluate factor levels in the 8th month of pregnancy to determine peripartum treatment plan

nancy, the VWF level increases and is often normal in the third trimester of pregnancy. VWF levels should be assessed in the 8th month to determine need for prophylaxis at delivery. Women should be made aware that postpartum bleeding may be delayed[26,48] and seek treatment if needed. For surgery, heparin and antiplatelet drugs should be avoided, and hemostatic agents should be continued 10-14 days, and for minor surgery, 3-5 days.[49,50] Cryoprecipitate cannot be virally inactivated without loss of activity and thus should be avoided.

Treatment—hemostatic agents

There is no consensus on the treatment of menorrhagia (**Table 8**). Oral contraceptives (OCPs), the first-line treatment for menorrhagia,[51] were reported to be ineffective in 76% of women with bleeding disorders referred to a hematologist,[25] despite reported reduction in blood loss and iron deficiency anemia.[52] Nonetheless, multiple formulations of combined hormonal contraceptives are available, and moderate-dose estrogen, if not used initially, may be tried if a low-dose estrogen pill fails to control menorrhagia. Continuous combined hormonal contraception may also be considered, in collaboration with a gynecologist, to induce temporary amenorrhea, although migraine headaches or cardiovascular disease may limit the use of estrogen. Whether the same incidence of long-term cardiovascular effects known to occur with hormonal therapy are reduced in women with VWD is not known.

The synthetic vasopressin analogue, DDAVP, or 1-desamino-8-D-arginine vasopressin, is the major hemostatic agent in type 1 VWD,[53] which acts through cyclic AMP-mediated release of VWF from endothelial Weibel-Palade stores.[54] Over 90% of patients respond to DDAVP at a dose of 0.3 μg per kilogram by intravenous infusion over 30 minutes, and although effective for mucosal bleeding, DDAVP may not reduce menorrhagia, as shown in a randomized placebo-controlled trial in women with bleeding disorders.[55] The intranasal form of DDAVP, Stimate®, given at 150 μg, or 0.1 mL of 1.5 mg/mL solution, one puff in one nostril for those < 50 kg in weight, and one puff in each nostril, for those ≥ 50 kg in weight, may also reduce menorrhagia when given as an adjunct to hormonal therapy.[56] Use of these agents is limited by tachyphylaxis, after depletion of endothelial stores, and adverse effects include tachycardia, headache, flushing, and rarely, hyponatremia or volume overload, due to antidiuretic effects, which are pre-

vented by avoiding excess fluid intake. Antifibrinolytic therapy, e.g., Amicar (epsilon aminocaproic acid), at a dose of 50 mg/kg every 6 hours for 5-7 days of the cycle, may reduce menorrhagia when used as an adjunct to hormonal therapy or DDAVP.[52]

The alternative to DDAVP for hemostasis in type 1 VWD is plasma-derived VWF-containing concentrate, which may reduce menorrhagia,[52] when given intravenously during the first 3-5 days of the cycle at a dose of 40-70 U/kg based on VWF:RCo activity.[49,50] Use of VWF-containing products, however, is limited by high cost, inconvenience, and potential transmissible infection risk. If blood products and hormonal therapy fail to control menorrhagia, surgical interventions may be considered, although the commonly attempted dilation and curettage (D&C) fails to reduce blood loss in women with bleeding disorders, and endometrial ablation, which induces temporary amenorrhea, may provide only short-term relief.[57] For these procedures or hysterectomy, DDAVP or VWF-concentrates will be required.

A potential new therapeutic approach is interleukin 11 (Neumega®) rhIL-11), a gp-130 signaling cytokine with hematopoietic and anti-inflammatory activities, which has increased VWF levels in VWD mice[58] and VWD dogs[59] and is currently in clinical trials.

Bleeding Disorders in Premenopausal Women—The View from Society

~Vincent J. Picozzi

There can be no doubt that the millions of premenopausal women with bleeding disorders experience significant and numerous compromises in lifestyle as a result of their disease. Numerous improvements in our public health approach to this problem seem necessary in order to improve healthcare outcomes for these patients.

The first necessary improvement would seem to be improved patient self-awareness of the potential existence of a bleeding disorder. Based on a recent study in which 1410 teenage girls in Sweden were surveyed by questionnaire for their bleeding history,[60] the prevalence of women in the population at risk for a bleeding disorder is far greater than the number that have actually been diagnosed. How best to educate and remind women as to the existence and characteristics of these disorders (e.g., health classes in school, public health messages) needs to be actively explored.

The second necessary improvement is for obstetrician-gynecologists and other primary care providers who see premenopausal women with bleeding disorders to become more aware of the possible existence of bleeding disorders in their patients. The mere existence of practice guidelines is inadequate for this purpose. Other forms of physician behavior modification (e.g., physician thought leaders, postgraduate education programs, practice benchmarks and reporting) will be necessary to accomplish this.

The third necessary improvement is for the hematology community to insure an adequate supply of well-trained, highly visible subspecialists willing and able to see such patients. An ongoing relationship between appropriate subspecialty groups concerning this health care issue and a national directory (geographically organized) of appropriate hematology providers would provide steps in this direction.

The fourth necessary improvement would be the development of improved screening tools for the detection of pathological bleeding (especially in VWD) for premenopausal women. The absence of a quantitative, definitive predictor of bleeding among currently available laboratory tests represents a major clinical limitation. The laboratory and clinical tools cited in this symposium represent a step in this direction, but such tools require ongoing testing and refinement "in the field" to assess their true utility. A better understanding of the overall screening process and studies of the cost-effectiveness of screening (including the implications of false-positive results) are clearly needed. Also needed are well-designed clinical studies to help physicians define the optimal diagnostic algorithms and clinical management for women with menorrhagia.

Finally, improved therapeutic approaches to VWD and other bleeding disorders important to premenopausal patients are clearly needed. A widely available roster of clinical studies appropriate to this hemostatic disorder, coupled with a broader network of clinical collaborators, would assist in the expansion of knowledge surrounding this important public health issue.

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