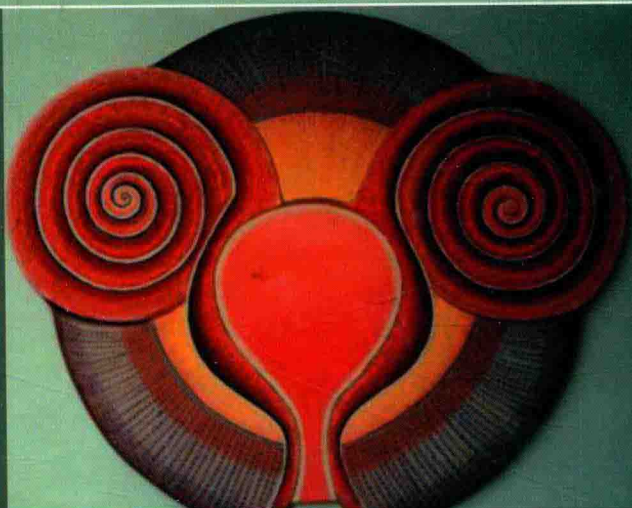


Inherited Bleeding Disorders in Women



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Preface

In 1926 Erik von Willebrand described a large kindred from the Aland Islands, an archipelago in the Baltic sea, many of whom had a bleeding disorder. The index case was a little girl called Hjordis, who presented with severe epistaxis and died at the onset of her fourth menstrual period. Her maternal grandmother died from haemorrhage after childbirth in her only pregnancy. von Willebrand wrote that the condition was particularly prevalent in women. This first description of von Willebrand disease underlined the haemostatic challenges of menstruation and childbirth for those women with an inherited bleeding disorder.

Until recently, the predominant issue for men with haemophilia has been safe and effective treatment, and most effort has been directed to the resolution of transfusion-transmitted disease. Furthermore, since haemophilia is a sex-linked disorder there has been a failure to recognise that women have inherited bleeding disorders. Thus, the substantial morbidity caused in women with inherited bleeding disorders has only recently been addressed in a comprehensive way. It is important that collaboration in the care and research of bleeding disorders in women continue as many challenges remain. The main task now is to identify those women who do not realise they may have a treatable condition. The patient advocacy organisa-

tions are crucial to this endeavour. There also remains the challenge of developing more effective, tolerable and widely available therapies in controlling menorrhagia and post-partum haemorrhage.

This book is written by haematologists, obstetrician-gynaecologists, an anaesthetist and those involved in patient advocacy. It covers the gynaecological and obstetric issues for carriers of haemophilia, women with von Willebrand's disease, rare bleeding disorders and inherited platelet disorders. We hope that this book is a modest step towards safe motherhood and provision of quality of care for women with bleeding disorders world-wide and that all those providing care for these women, as well as the women themselves, will find it useful.

Acknowledgement

Cover image 'Menorrhagia Healing' © Barbara Bruch 1991

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1 Approach to the patient with an inherited bleeding disorder

Peter A Kouides and Claire Philipp

Introduction

At the time of injury to the endothelium, the integrity of the high-pressure circulatory system is maintained through the hemostatic mechanism. In general terms, a “plug” of platelets is covered over by a “net” of fibrin, resulting in the formation of a clot (Fig. 1.1). The resultant clot normally leads to cessation of bleeding. Bleeding occurs when there is a precipitant such as direct traumatic injury to the endothelium or in the case of menstruation hormonal-induced shedding of the endothelium, so “injuring” the endothelium.

The understanding of hemostasis can be simplified into two steps: first (step 1) the formation of the platelet “plug” at the initial site of injury and second (step 2) the formation of a “net” of fibrin covering the platelet plug. An evolving cell-based model of hemostasis augments the historical description of coagulation focused on enzymatic activation of a sequence of coagulant proteins as a “cascade.” The cell-based model includes the crucial role of tissue factor (TF)-bearing cells at the site of bleeding [1, 2]. The two main components within the blood exposed to the injured endothelium in step 1 are von Willebrand factor (VWF) and platelets. At the time of vessel injury, there is exposure of free-flowing blood through the injured endothelium to two subendothelial constituents, collagen and TF, involved respectively in platelet plug formation and fibrin generation.

Formation of the platelet “plug”

The flowing blood is subjected to a high shear stress rate upon exposure of subendothelial collagen following injury to the endothelium. The high shear stress leads to “unfolding” of VWF with subsequent exposure of the A1 and A3 domains [3]. The A1 domain primarily recognizes and binds to the glycoprotein Ib_α/IX receptor on the platelet surface whereas the A3 domain primarily recognizes and binds to subendothelial type I and type III collagen [3]. In essence, VWF localizes the platelets to the site of bleeding by binding to collagen and also to platelets that are traveling through the injured opening of the endothelium. The VWF protein is capable of binding to both platelets and collagen because it is a large, multimeric molecule. The binding of platelets to collagen by VWF leads to the subsequent aggregation and formation of a platelet plug.

Formation of fibrin

Adequate clot formation is necessary to fully stop bleeding; thus, a patient with a clotting factor deficiency, such as hemophilia, bleeds even though the platelet count and function and VWF are normal. At the time of injury factor VIIa (FVIIa) within the flowing blood at the injured site is exposed to subendothelial TF. This imitates thrombin generation resulting in fibrin formation. This leads to the formation of the VIIa–TF complex on the surface of platelets which are acting as a “scaffold,” and then converts FX to activated FXa (termed the “extrinsic pathway” as depicted in Fig. 1.2). In turn, FXa is localized to the

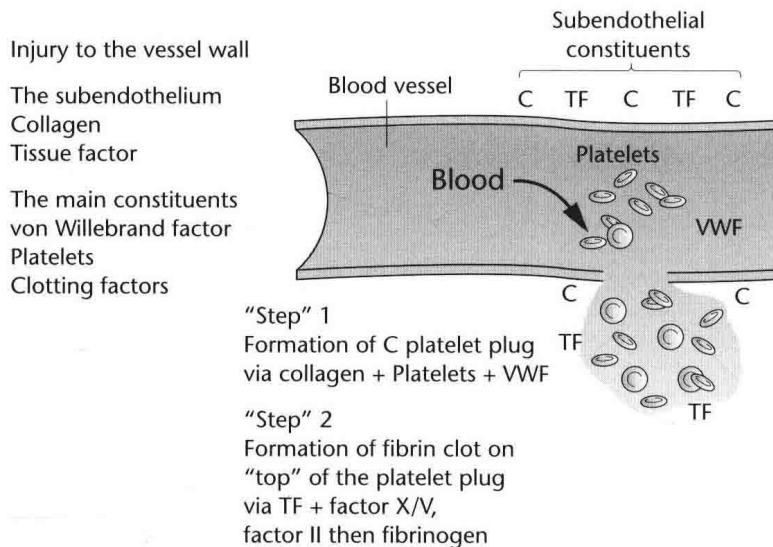


Fig. 1.1 Steps in hemostasis. C, collagen; TF, tissue factor; VWF, von Willebrand factor.

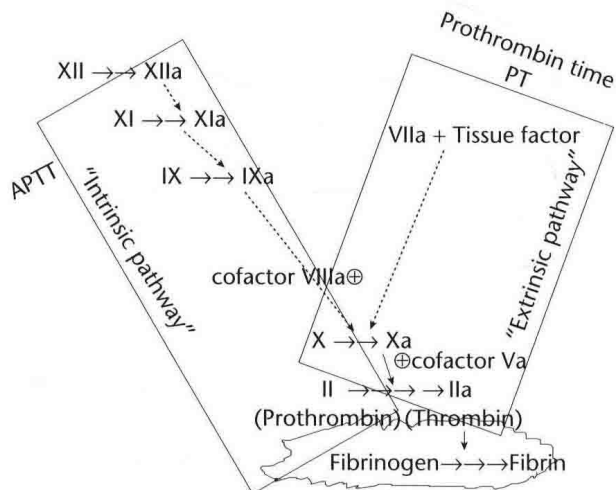


Fig. 1.2 The pathways of coagulation: the intrinsic (*in vitro*) pathway as measured by the activated partial thromboplastin time (APTT) and the extrinsic (*in vivo*) pathway as measured by the prothrombin time.

platelet surface by the cofactor, factor V (FV). This enzyme complex of FX + FV can then convert circulating coagulation factor II (prothrombin) to IIa (thrombin). Thrombin is the main enzyme of the coagulation cascade, and cleaves circulating fibrinogen to fibrin, which polymerizes to form a "net" of fibrin around the platelet plug. Patients with a deficiency of FVIII (hemophilia A) or FIX (hemophilia B) bleed even though these patients should have an adequate amount of FVII as well as FII, FV, FX, and fibrinogen.

This is because such patients do not have amplification of the coagulation cascade by FIX with cofactor VIII. The FIX/FVIII complex activates X to Xa, and is termed the propagation phase of coagulation.

Bleeding: inherited platelet disorders and von Willebrand disease

A quantitative defect of platelets (thrombocytopenia) as in the case of immune thrombocytopenic purpura (ITP) or acute leukemia, or a qualitative defect (i.e., dysfunction) of platelets ("thrombocytopathy") as in the case of uremia or aspirin use can lead to bleeding. Another cause of bleeding related to step 1 of hemostasis would be a quantitative or qualitative deficiency of VWF termed von Willebrand disease (VWD). von Willebrand disease is an inherited bleeding disorder. A mild to moderate (~15–50% VWF level) deficiency with normal multimer structure of VWF is termed type 1; a qualitative deficiency with dysfunctional VWF is type 2 [4]. In type 2, the qualitative defect can be classified further as a loss of high and intermediate weight multimers (type 2A); a loss of high molecular weight multimers (type 2B) usually with associated thrombocytopenia; or normal VWF multimers (type 2M). Type 2N VWD involves a mutation leading to decreased binding of FVIII with resultant FVIII deficiency and this is often misdiagnosed as hemophilia A. Finally, a severe quantitative deficiency of VWF with undetectable VWF protein is termed type 3.

The severe forms of VWD usually have a detectable genetic mutation whereas a third to a half of cases of type 1 VWD have a normal genotype implying extragenetic factors in the pathogenesis of VWD in these cases [5, 6]. Many of these cases (usually with VWF levels ~30–50%) with a normal genotype are related to ABO blood group O [7]. In turn, 15% of ABO blood group O patients have VWF levels <50% [8]. Consequently, given the ~40% prevalence of blood group O in the general population, ~5% of the general population will have “subnormal” VWF levels.

Bleeding: inherited coagulation factor deficiencies

Bleeding may result from a deficiency of any of the clotting factors of the coagulation cascade from factor I (fibrinogen) to factor XI. Inherited clotting factor deficiencies are due to a mutation in the gene coding for the respective coagulation protein resulting in a lower than normal level adequate for hemostasis.

Clinical presentation of the bleeding patient

Inherited platelet disorders and VWD are associated with “mucocutaneous” bleeding. Typical bleeding frequently involves nosebleeds (epistaxis), bleeding related to surgical invasive procedures including dental work, easy bruising and menorrhagia. In contrast, patients with an inherited coagulation factor deficiency such as hemophilia will have primarily deep tissue (ecchymoses) and muscle/joint bleeding. A previously undiagnosed mild disorder such as mild hemophilia A with a low factor VIII level can be “unmasked” in the setting of surgery.

Table 1.1 The prevalence of various bleeding symptoms in the general population, adapted from Sadler [9] with permission

Symptom	Healthy controls (%)
Epistaxis	5–39
Gum bleeding	7–51
Bruising	12–24
Bleeding from trivial wounds	0.2–2
Dental extraction related bleeding	1–13
Post-tonsillectomy bleeding	2–11
Post-partum bleeding	6–23
Menorrhagia	23–44

The challenge for the clinician when encountering the bleeding patient is to determine whether the bleeding symptom is due to an underlying disorder of hemostasis. Many bleeding symptoms may be quite prevalent in the general “healthy” population with a prevalence of bleeding symptoms reported ranging from 0.2% (bleeding from trivial wounds) to 51% (gingival bleeding) [9] as summarized in Table 1.1. However, only a relatively small proportion of these patients will have a true underlying disorder of hemostasis. Consequently, the discriminatory power of the various bleeding symptoms in predicting an underlying disorder of hemostasis varies from poor to excellent as depicted in Table 1.2, based on the authors collective clinical experience and published studies of bleeding risk [9–12].

These symptoms have been refined and incorporated into a scoring system (termed the bleeding score assessment) by the International Society of Hemostasis and Thrombosis network [13] and then modified by the European Union VWD project [14] (Appendix i). The main principles underlying this bleeding assessment

Table 1.2 The relative discriminatory value of bleeding symptoms

Good	Fair	Poor
Family members with established bleeding disorder	Bruising	Family members with bleeding symptoms
Profuse bleeding of small wounds	Epistaxis	Gum bleeds
Profuse surgical-related bleeding esp. T&A, dental	Menorrhagia	Hematuria
Muscle/joint-related bleeding	Post-partum hemorrhage	Bright blood per rectum

T&A, tonsillectomy and adenoidectomy.

are that the likelihood of a laboratory diagnosis of VWD is increased if (a) the bleeding symptom is of such severity that medical attention was sought and/or an intervention made, or (b) multiple bleeding symptoms are present. Ten bleeding symptoms were graded from 0 to 3 and, in general, a score of 2 was given if the respective bleeding symptom required medical attention whereas a score of 3 indicated the symptom necessitated a medical intervention. If the resultant total score was >3 in males or >5 in females, the sensitivity, specificity, and positive and negative predictive values for type 1 VWD were respectively 45%, 100%, 100% and 99.5 %. Subsequently, in a further modification of the bleeding score assessment tool, a -1 score was introduced to account for situations associated with a high bleeding risk, such as tooth extraction, where bleeding did not occur even though prophylaxis was not given. On further analysis, an inverse relationship was noted between the score and the VWF levels [14].

Studies are ongoing to determine the utility of the bleeding score in the diagnostic evaluation of other hemostatic disorders, such as platelet function defects, and in the pediatric population [15].

Recent studies demonstrate that nearly 50% of “idiopathic” menorrhagia patients will have a laboratory abnormality of hemostasis, including most frequently VWD or a platelet function defect [16, 17]. If we assume that knowledge of such an abnormality will have clinical benefit, then it becomes a public health issue [18] to test for disorders of hemostasis in all menorrhagia patients. Thus, modifications of the EU bleeding score (range -3 to 45) [13, 14] or other assessment tools [19] for screening women may be a cost-effective measure. In 42 women with documented VWD in London, the mean bleeding score was 9.7 compared with a mean score of 0 in 10 control subjects, a resultant sensitivity of 83% for a bleeding score >5 [20].

A recently developed screening tool appears promising in identifying which women with menorrhagia warrant referral for comprehensive hemostatic testing [19]. Based on analysis of a 12-page bleeding and menstrual symptom questionnaire in 146 menorrhagia patients undergoing hemostasis testing [21], there was a relatively high sensitivity of 81% (95% CI 74–89%) and positive predictive value 71% (95% CI 63–71%) if one of the following four criteria were met: (a) duration of menses >7 days and either “flooding” or

impairment of daily activities with most periods; (b) a history of treatment of anemia; (c) family history of a diagnosed bleeding disorder; (d) history of excessive bleeding with tooth extraction, delivery or miscarriage or surgery. Furthermore, the addition of a pictorial blood assessment chart score (see Appendix ii) >100 increased the sensitivity of the screening tool to 93% (95% CI 89–98%) [19].

Since VWD and platelet function defects are the most common bleeding disorders in females [21, 22], the bleeding symptoms associated with these disorders of hemostasis will be discussed in further detail.

Epistaxis

This occurs predominantly in childhood and decreases in frequency and severity as the patient enters adulthood [23]. Epistaxis is “significant” if excessive bleeding necessitates medical attention, particularly packing and/or cautery. The typical duration is >10 minutes and the typical frequency is at least yearly, particularly in childhood, adolescence and young adulthood.

Dental work-related bleeding

Excessive bleeding at the time of wisdom tooth extraction or other invasive dental procedures is associated with bleeding disorders. A history of intervention by the dentist for continued/recurrent bleeding after dental extraction is probably significant [13].

Skin-related bleeding

This includes easy bruising and bleeding from trivial cuts.

Bruising Bruising is a very subjective bleeding symptom and a significant proportion of women in a general primary care practice report easy bruising. In one study 24% of reproductive age control women compared with 78% of women with VWD reported easy bruising [24]. Significant features of bruising appear to be: (a) atraumatic bruising, (b) bruising occurring at least weekly, and (c) bruises greater than 5 cm.

Bleeding from cuts Prolonged bleeding >5 minutes from trivial cuts [13] such as a paper cut or shaving appears to be significant.

Menorrhagia

Menorrhagia is the most common symptom in females with VWD. Approximately 80% of patients with

VWD report that they regard their periods as heavy [24–26]. Women with a deficient amount of VWF protein are unable to form adequate platelet plugs and formation of the platelet plug is critical in resolving menstrual blood loss. Consequently, the pre-test probability of “true” menorrhagia (>80 mL blood loss per menstrual cycle objectively documented by spectrophotometric analysis of collected pads and tampons) would appear to be quite high in a female with VWD. This is unlike the general population of females reporting a history of menorrhagia, where the positive predictive value of excessive menstrual loss may be anywhere from 25% to 75% [27]. In the (general) female population, a complaint of menorrhagia requiring a trial of oral contraceptive does not reliably predict excessive menstruation by objective measurement [28]. Table 1.3 outlines features that probably have a positive predictive value for menorrhagia in patients with VWD reporting heavy menses.

Menstrual blood flow can be measured objectively by the spectrophotometric method, which involves

collection of all menstrual pads and dissolving them in an alkaline solution to convert the heme into hematin. Surrogate estimates of menstrual blood flow have been developed using the pictorial blood assessment chart [29], as described further in Appendix ii. Iron deficiency anemia may correlate with true menorrhagia and is present in at least two-thirds of women with menorrhagia [30]. Serum ferritin status, clots, and the pad changing rate have been demonstrated to be predictive of objectively defined menstrual loss in 76% of women [28].

Postpartum hemorrhage

A >500 mL loss of blood occurs in the first 24 hours following delivery in about 4% of the general population whereas blood loss after 24 hours greater than the normal “lochia” loss occurs in 1.3% of the general population [31]. Hemostasis testing should be performed in patients if there is a family history of bleeding or a history of postpartum hemorrhage (PPH) so severe that it necessitates blood transfusion. In a survey of type 1 VWD patients, one-quarter required red blood cell transfusions [24].

Table 1.3 The salient details of menses in women with bleeding disorders.

Audit of prior medical interventions

? history of hormonal therapy, dilation and curettage, endometrial ablation, levonorgestrel intrauterine device, hysterectomy

Details of menses

? use of (super) absorbent pads
 ? use of two pads or tampons at a time or both
 ? changing pad or tampon q 0.5–2.0 hours
 ? frequently stain clothes or bed sheets
 ? clots the size of a quarter (pence)
 ? time lost from work/school
 ? iron requirement

Quality of life assessment: on a scale of 0 to 10, to what degree, if any, does menses interfere with general activity

Ability to go to work or school
 Family activities
 Ability to enjoy life
 Sleep
 Mood
 Overall quality of life

Pain assessment

? mid-cycle pain
 ? degree of pain during menses

Approach to a female who has a “positive” bleeding history

The bleeding history is important in the diagnosis of a bleeding disorder. Laboratory assessment is required to confirm the diagnosis. A synthesis of the history, physical examination and laboratory assessment is presented in Fig. 1.3.

History

The history should include (a) the patient’s past and present history of bleeding symptoms, and (b) a family history of bleeding.

A past personal history of bleeding is suggestive of an inherited bleeding disorder. The history should include easy bruising, prolonged bleeding with trivial cuts, extensive oral cavity bleeding, epistaxis, bleeding at the time of dental work or any surgical procedure, PPH, and menorrhagia (as depicted in Table 1.4).

A positive family history suggests an inherited bleeding disorder. Even though VWD is inherited, there can be variable penetrance as well as spontaneous mutations, and the patient may not have a family history

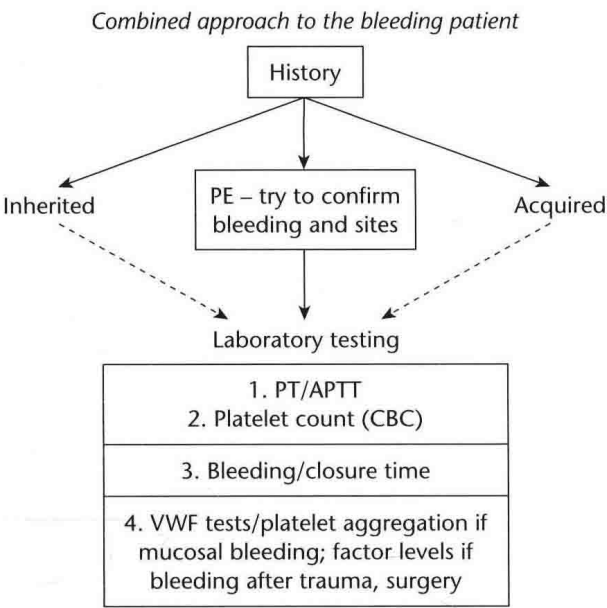


Fig. 1.3 The synthesis of the history and laboratory examination in a patient with a suspected bleeding disorder. PE, physical examination; PT, prothrombin time; APTT, activated partial thromboplastin time.

of excessive bleeding. If the family history for bleeding is limited to males, females may be carriers of the hemophilia gene. Female carriers of the hemophilia gene can be symptomatic and themselves manifest mild symptoms [11] (see Chapter 3).

Physical examination

If the patient reports bruising, this can be confused with a drug-induced rash, rash from another cause, or skin discoloration [32]. A distinction has been made between bleeding from a platelet/VWF deficiency and bleeding from a coagulation factor deficiency. The former patients will have “mucocutaneous bleeding”; therefore, careful examination of the nose and gums are important. The latter patients will have a tendency to bleed in the joints and deep tissue, requiring careful examination for joint swelling or even contracture formation.

It is possible that a patient, particularly with VWD, may unmask an underlying anatomical/pathological lesion in the uterus and the pelvic examination may be abnormal [24, 25, 33, 34].

Table 1.4 Suggested list of symptoms for history taking of the bleeding patient

Bleeding symptoms	Ever experienced symptom?		If yes, provider intervention required ever?	
	Yes	No	Yes	No
More than one nosebleed per year lasting 10 minutes or longer	☐	☐	☐	☐
Oral mucosal bleeding lasting 10 minutes or longer	☐	☐	☐	☐
Bleeding during or after dental procedures of concern to healthcare provider	☐	☐	☐	☐
Bleeding from minor cuts lasting 5 minutes or longer	☐	☐	☐	☐
Bruises larger than a quarter size occurring at least once a month without trauma	☐	☐	☐	☐
Bleeding after surgery of concern to healthcare provider	☐	☐	☐	☐
Menstrual bleeding that required protection change at least every 2 hours on heaviest day	☐	☐	☐	☐
Bleeding with pregnancy/post-partum of concern to healthcare provider	☐	☐	☐	☐
Joint bleeding	☐	☐	☐	☐
Muscle bleeding	☐	☐	☐	☐
Central nervous system bleeding	☐	☐	☐	☐
Gastrointestinal bleeding	☐	☐	☐	☐

Laboratory assessment

Accurate hemostasis testing is important because the specificity of bleeding symptoms may be poor, and many “normal” patients without an identifiable disorder of hemostasis will report bleeding symptoms [9, 24].

Initial screening tests in the female with a “positive” bleeding history would include the following.

- 1 Full blood count (FBC): iron deficiency can first be detected by a decreased mean cell volume (MCV). The FBC includes a platelet count.

- 2 Prothrombin time (PT), activated partial thromboplastin time (APTT): these are standard, readily available tests of hemostasis carried out in the evaluation of the bleeding patient. However, in general, these tests carry a very low positive and negative predictive value for an underlying bleeding disorder [35].

Clinicians generally use the FBC and PT/APTT in the evaluation of a patient who presents with a bleeding history with the erroneous assumption that normal PT/APTT values rule out an underlying bleeding disorder. Whereas the sensitivity of a prolonged APTT for VWD is less than 40% [36], for the severe recessive clotting factor deficiency, factors I, II, V, VII, X, XI, the PT and APTT are an adequate screen [37].

A prolonged APTT necessitates a mixing study with pooled normal plasma to distinguish further between a deficiency state such as hemophilia or an inhibitor. An inhibitor, such as a lupus anticoagulant or acquired hemophilia A, a potentially life-threatening bleeding diathesis, would not demonstrate a corrected APTT on mixing with normal plasma.

- 3 VWF testing (VWF antigen, VWF ristocetin cofactor and factor VIII levels). The ~13% (95% CI 11.1–15.6%) prevalence [22, 38–41] of VWD in females with menorrhagia warrants VWF and FVIII levels as part of the initial hemostasis evaluation. The FVIII level can be reduced in VWD as VWF protects FVIII from proteolytic cleavage [42]. Factor VIII deficiency with normal VWF levels may also be associated with menorrhagia (i.e., female carriers of hemophilia A, von Willebrand Normandy) [11, 25].

VWF analysis ideally should be done on site with immediate on-site processing. Frequent misdiagnosis of VWF deficiency occurs when specimens are transported to another site far from where the blood was drawn with subsequent activation/degradation of the sample [43]. In the USA, this is a growing concern among hematologists because VWF levels are drawn

through managed care contracted laboratories where the plasma sample may be sent thousands of miles away and be exposed to extreme temperatures [43]. Cold storage of whole blood can lead to artifactually low VWF levels [44]. Such patients may then be given an erroneous laboratory diagnosis of VWD that ultimately is disproved on referral to the hematologist/laboratory scientist capable of on-site processing and complex analysis of the plasma sample. Ideally, primary care physicians should refer the patient directly to a hemostasis laboratory.

Furthermore the clinician must be aware that VWF and FVIII levels can fluctuate during the menstrual cycle. The use of exogenous hormones such as the oral contraceptive (OC) may change these levels [45]. The laboratory diagnosis of VWD is discussed further in Chapter 4.

Testing in relation to the menstrual cycle

There have been reports in a relatively small number of patients that show a decrease in VWF levels during menstruation [46, 47]. The practitioner should note the time in the menstrual cycle of VWF testing and whether the results are at the mean or below the reference range. Repeat testing should be performed in the first 4 days of menstruation.

Testing and oral contraceptive use

It has been suggested that OC use can mask the diagnosis of VWD based on an observation that estrogen can raise VWF levels in patients with VWD [48]. However, there is a lack of evidence demonstrating a definite effect of the current combination OCs (which are of lower dose potency than the estrogen preparations used in the initial case reports associating estrogen with raising the VWF levels). A practical approach would be to test women prior to starting the OC, if possible, but to obtain VWF testing if OCs have already been started.

Adjustment for the ABO blood type

It is well known that patients with blood type O have 25% lower VWF and FVIII levels [8]. Adjusting normal ranges for ABO blood type would require a lower threshold VWF and FVIII level for blood type O patients with bleeding symptoms. However, it has

been shown that type O patients with VWF levels between 35% and 50% had similar bleeding symptoms to non-O patients in that range [49]. Whether the laboratory diagnosis of VWD necessitates ABO adjustment remains controversial. Probably a significant proportion of cases that have been diagnosed as mild "VWD" are non-genetic and related to the blood type [50]. Perhaps, in the future, a better descriptive term of patients with subnormal VWF levels and bleeding symptoms would be the classification of von Willebrand deficiency based on the demonstration of a subnormal VWF antigen and/or ristocetin cofactor compared with the non-ABO-adjusted local laboratory range [51]. ABO typing may still be advisable, as the finding of blood type O allows the clinician to emphasize to the patient that their subnormal VWF level is most likely secondary, at least in part, to being blood type O. Recent US guidelines do not advise ABO adjustment [52].

In those patients with a low VWF antigen and/or ristocetin cofactor VWF multimer analysis and ristocetin-induced platelet aggregation should be carried out for further subtyping of VWD [45].

Because of the association of hypothyroidism with acquired VWD, the patient should be screened for hypothyroidism [53, 54]. In hypothyroidism, thyroid replacement can result in resolution of the VWF deficiency [55].

Bleeding time and/or platelet function analyzer-100 closure time

The bleeding time (BT) and the platelet function analyzer-100 closure time (CT) have a relatively poor sensitivity for mild VWF deficiency [56] and platelet function disorders [56–58]. However the platelet function analyzer-100 CT may be useful for monitoring treatment [59].

Platelet aggregation and release studies

If initial hemostasis testing is normal, platelet aggregation and release, preferably off all medication, should be performed [60]. This is warranted on the basis of a relatively high prevalence of platelet function abnormalities in patients with menorrhagia. The abnormalities were far more prevalent in the black population [21]. Such a patient may respond to desmopressin [61] and shortening of the CT can be seen [62].

Additional coagulation studies may be considered if platelet aggregation and release studies are within normal limits. This would include testing for factors II, V, VII, X and XI deficiencies. Approximately 1–4% of women with menorrhagia have been found to have mild single factor coagulation deficiency other than VWD [16, 18, 37]. Additional coagulation studies such as testing for factor XIII deficiency [37] and tests for fibrinolysis such as the euglobulin lysis test [63] and more specific assays for α_2 -anti-plasmin or plasminogen activator inhibitor deficiency may be indicated. Increased fibrinolysis, in general, has been reported in menorrhagia patients [64–66], but whether fibrinolysis is localized to the uterus or present systemically has not been fully studied. Patients with bleeding diatheses, including menorrhagia, associated with deficiencies in plasminogen activator inhibitor 1 and α_2 -plasmin inhibitor have been reported [67–69].

Finally, when all of the above tests for hemostasis return normal, the clinician should reconsider the history in terms of a bleeding disorder. In particular, it is possible that what the patient reports as bruising is a drug-induced rash or a disorder of the endothelium, such as scurvy or vasculitis, or a connective tissue disorder, such as hereditary hemorrhagic telangiectasia. If all these possibilities are absent, the patient may have a disorder of hemostasis yet undiscovered and on occasion in cases with a very convincing bleeding history, e.g., multiple mucocutaneous bleeding symptoms of severity necessitating medical attention/intervention in the past, consideration for semi-empiric hemostatic therapy can be considered at the time of invasive procedures.

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