

Systemic Causes of Excessive Uterine Bleeding

Jeanne M. Lusher

Introduction

In addition to strictly gynecologic causes, a number of systemic conditions can result in bleeding problems in women. These include both hereditary and acquired disorders of coagulation factors and/or platelets. In evaluating a woman with excessive bleeding, primary care providers as well as medical specialists should consider these systemic causes in their differential diagnosis. The most common of these is von Willebrand disease; however, a brief description of other entities to be considered will also be presented.

von Willebrand Disease

von Willebrand Disease (vWD) is the most common of the hereditary disorders of coagulation, affecting an estimated 1% of the population world wide.⁽¹⁻³⁾ vWD affects all racial groups. While there is a wide spectrum of severity among affected individuals, it is thought that at least 10% of these have excessive bleeding.⁽⁴⁾ vWD is characterized by mucous membrane bleeding, excessive bruising, and excessive bleeding following surgery or invasive procedures. This disorder was first described by Dr. Erik von Willebrand of Helsinki, Finland in the 1920s. Dr. von Willebrand studied a large kindred on the Åland Islands in the Gulf of Bothnia, off the coast of Sweden. While both males and females had a bleeding tendency, the young women were more severely affected, with menorrhagia being a major problem in many of them. In one family, 5 of 7 daughters had bled to death, one during her fourth menstrual period. By today's standards, Dr. von Willebrand had only crude methods of studying this large kindred; however, he noted that their bleeding times were prolonged while their platelets appeared normal.⁽⁵⁾ For a number of years thereafter, the diagnosis of von Willebrand disease was based on the findings of excessive mucous membrane bleeding, a prolonged bleeding time with normal platelet count, and an autosomal dominant mode of inheritance.

With today's more sophisticated diagnostic tests (see **Table 1**), one can often document not only that a person has vWD, but what type and subtype of vWD they have. We now know that the underlying abnormality in vWD is in von Willebrand factor (vWf), a large, multimeric adhesive plasma protein.⁽⁶⁻⁸⁾ In the Type 1 variants, the vWf which

the individual produces is normal in structure and function, but not enough is produced. In contrast, in the Type 2 variants, the vWf produced is structurally (**Figure 1**) and functionally abnormal. In the Type 3 variants, in which the affected individual has inherited a gene for vWD from each parent, very little or no ($\leq 3\%$ of normal amounts) vWf is produced^(9,10) (see **Figure 2** and **Tables 2** and **3**).

It is very important not only to *suspect* the possibility that a woman has vWD, and to establish the diagnosis, but also to determine the *type* of vWD she has, as treatment differs depending on the type^(11, 12) (see below).

Functions of von Willebrand Factor

von Willebrand factor has two major functions. Most importantly it acts as a "bridge" between platelets and injury sites in the vessel wall. The high molecular weight multimers are most important in this regard. In addition, vWf circu-

Table 1 Diagnostic Tests for Suspected vWD

- Ristocetin cofactor (vWf:RCo) assay
- F VIII
- von Willebrand factor antigen (vWf:Ag)
- Template bleeding time (may or may not be abnormal)
- Multimeric analysis of vWf (using SDS agarose gel electrophoresis)

Table 2. Classification of von Willebrand Disease*

Type	Characteristic Features
1	Partial quantitative deficiency of vWf
2A	Qualitative variants with loss of high molecular weight multimers of vWf
2B	Qualitative variants in which the higher molecular weight (MW) multimers of vWf have an abnormally increased affinity for platelets (platelet Gplb / IX complex)
2M	Qualitative variants with decreased platelet function but preservation of high MW multimers of vWf
2N	Qualitative variants with decreased binding of F VIII
3	Total (or near total) absence of detectable vWf with markedly decreased F VIII

* from Sadler JE: A revised classification of von Willebrand disease. *Thrombos Haemost* 71:520-525,1994.

Table 3. Characteristics of vWD

- Type 1 ("classic"): 80% of affected persons
- Usually have prolonged bleeding time
 - vWf:RCo, F VIII, vWf:Ag are proportionately decreased
 - vWf produced is structurally and functionally normal
- Type 2: 20% of patients
- vWf is functionally and structurally abnormal
- Type 3 (rare)
- vWf:Ag, vWf:RCo, and F VIII are undetectable or very low (< 3%)

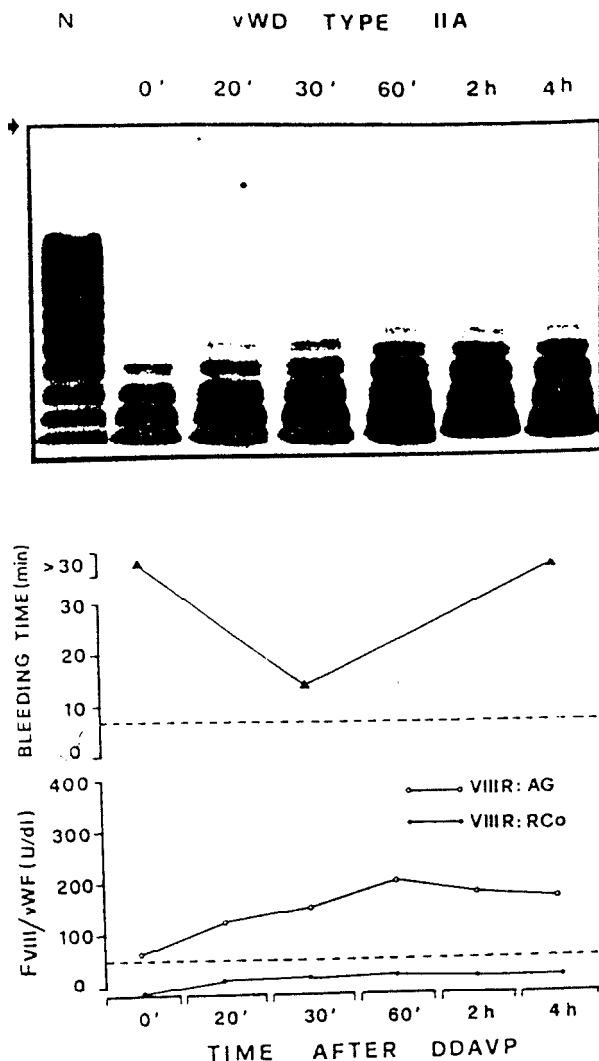


Figure 1. (Top) Autoradiograph pattern of plasma factor VII/von Willebrand factor from a patient with von Willebrand's disease type IIA, before (time 0) and at various times after infusion of DDAVP. The pattern of normal plasma (N) is shown for comparison on the extreme left lane. (Bottom) Quantitative changes of factor VII/von Willebrand factor and of the bleeding time observed at the same time.

Reprinted with permission from Ruggeri et al. Blood.⁽⁶⁾

Table 4 von Willebrand Factor (vWf) Levels are Influenced by Several Conditions (in addition to von Willebrand Disease)

- The individual's ABO blood type
Persons of blood type AB have 60-70% higher levels of vWf than do those of blood type O
- Stress, DIC, hyperthyroidism, pregnancy, oral contraceptives, collagen vascular disorders can elevate vWf levels
- Hypothyroidism will reduce levels

lates with F VIII and protects it from rapid proteolytic degradation in the circulation.⁽⁷⁾ Thus, if a person lacks vWf, their platelets will not adhere to injury sites in the vessel wall, and their F VIII level will be low (see **Figure 2**).

Diagnostic Approach

As in all aspects of medicine, a pertinent history (including family history) and physical examination are extremely important in evaluating the woman with excessive uterine bleeding. If the patient's history and physical examination reveal that she has (in addition to menorrhagia) epistaxis, gum bleeding, and/or excessive bruising, and has bled excessively with surgical procedures or invasive dentistry, one should have a high index of suspicion that she has vWD or an abnormality of platelets. Statistically, vWD, which affects ~ 1% of the population, would be much more likely. Since vWD usually has an autosomal dominant inheritance pattern, one can usually elicit a history of menorrhagia and/or other types of mucous membrane bleeding, excessive bruising, and/or excessive bleeding during and following invasive procedures, etc., in the woman's siblings, a parent, and other relatives. However, if the family history is negative, one should not *exclude* the possibility of vWD, as clinical severity varies among affected individuals, the patient may not be aware of the bleeding tendency of other family members, and the family may be small in numbers. Additionally, if all the women in her immediate family have heavy menstrual periods, this may be regarded by them as being normal.⁽¹³⁾

While a battery of diagnostic tests is generally recommended (see Table 1), many regard the ristocetin cofactor (vWf:RCo) assay as being the most useful. The vWf:RCo is our closest measurement of vWf function, and is abnormally low in almost all types of vWD (see Figure 2). The assay for vWf: RCo is based on the property of the antibiotic ristocetin to agglutinate platelets in the presence of vWf. It should be noted, however, that several other things can influence vWf levels (see **Table 4**). By performing the battery of tests shown in Table 1, one can usually determine that the patient has (or does not have) vWD, and usually can determine the type as well. However, diagnosing mild Type I vWD is often problematic, and repeat laboratory testing may be required.⁽⁴⁾ While the patient's activated partial thromboplastin time (APTT) may be abnormally prolonged, this will be dependent on the F VIII level. With most APTT reagents, the APTT will not be prolonged unless the F VIII is less than 0.30 U/ml (30%). The bleeding time (BT) is usually prolonged, but may be normal in mild, Type I vWD. Additionally, the sensitivity of the BT, F VIII assay and vWf:RCo assay are not very high.⁽¹⁵⁾

While most routine clinical coagulation laboratories do not perform multimeric analysis of vWf, an aliquot of plasma can be sent to one of several reference laboratories for this. Using low resolution sodium dodecyl sulfate (SDS) gels, radiolabeled antibody to vWf, and autoradiography, one can visualize the multimeric bands of vWf. In Type I vWD, all bands are present, while in the Type 2 variants (especially

Test	Type 1	Type 2A	Type 2B	PT-vWd	Type 2N	Type 2M	Type 3
vWf:Ag	↓	↓	± ↓	± ↓	↓	↓	Absent
vWf:RCo	↓	↓↓↓	± ↓	± ↓	↓	↓↓↓	Absent
FVIII	↓	Normal	Normal	Normal	↓↓	Normal	Absent
RIPA	± ↓	↓↓	Normal	Normal	Normal	↓	Absent
RIPA-LD	Absent	Absent	Increased	Increased	Absent	Absent	Absent
Frequency	70%–80%	10%–12%	3%–5%	0%–1%	1%–2%	1%–2%	1%–3%
Multimers:							

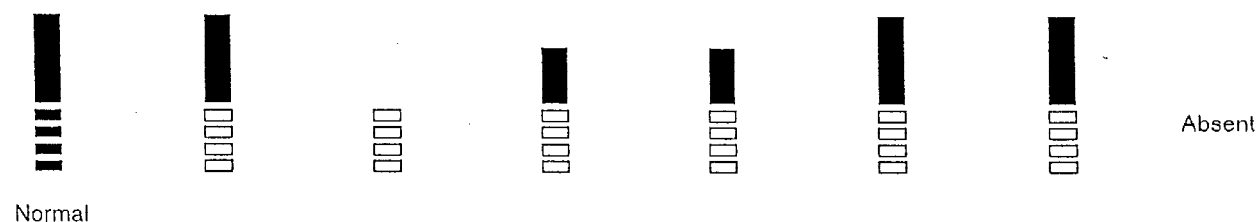


Figure 2. von Willebrand Variants.

types 2A and 2B), no high molecular weight multimers are seen.^(10,14,15) Exceptions to this are Type 2M (“M” for multimers) and 2N (“N” for Normandy) vWD; these Type 2 variants have a normal multimeric structure, but impaired platelet binding in the former and impaired F VIII binding in the latter.^(10, 15)

Treatment Considerations

Once the woman’s diagnosis has been established, appropriate management can be decided upon. This will depend on the type and severity of vWD, and the hemostatic challenge (i.e., surgery, invasive dentistry, severe menstrual bleeding, gastrointestinal bleeding, severe epistaxis). Most (80%) persons with vWD have Type I vWD, which is the easiest to manage once the diagnosis has been made. The treatment of choice is desmopressin acetate (1-deamino-8D-arginine vasopressin; DDAVP). This synthetic analog of the naturally occurring antidiuretic hormone, vasopressin, when given intravenously (IV) in the recommended dosage of 0.3 mg/kg body weight, will effect an almost immediate 3-5 fold⁽¹²⁾ (range 2-8 fold) increase in circulating F VIII and vWf, as well as a transient correction of the BT. It is recommended that a test dose of desmopressin be given to each patient in order to document the response. While responses differ among individuals, they are generally consistent in the same individual over time. Thus, a woman who has a 5-fold increase in F VIII and vWf:RCo after a test dose of IV DDAVP will likely have a 5-fold increase when given the drug a few weeks later. Desmopressin is available in several formulations. While the parenteral form is generally used for surgical situations or other in-hospital use, a highly concentrated intranasal (IN) spray formula-

tion (Stimate nasal spray, distributed by Centeon, King of Prussia, PA) is ideal for home or out-patient use.^(1,16,17) Dosage with the IN spray formulation is one spray (in one nostril) for children and two sprays (one in each nostril) for adolescents and adults. Each activation of the metered dose spray pump delivers 0.1 mL, or 150 µg DDAVP. Adverse effects of DDAVP are generally minor in nature (e.g., facial flushing, facial warmth); however, the drug is a potent antidiuretic agent. Thus, there is a slight risk of hyponatremia, water intoxication and convulsions. Awareness of this risk, with avoidance of excessive fluid intake for 18 hours post-DDAVP, or avoidance of large amounts of hypotonic fluids post-operatively, should minimize the likelihood of this complication.

If repeated doses of desmopressin are needed for the same bleeding episode, these should be given at 12-24 hour intervals. Most persons treated repeatedly with DDAVP become less responsive by the second or third day, presumably due to transient depletion of the storage sites for vWF.^(12,18,19)

For *menorrhagia*, the IN spray formulation is ideal. In general, one or two doses will suffice. It is recommended that an initial dose of Stimate nasal spray be given at the onset of the woman’s menstrual period. If necessary, the dose can be repeated the next day. Many women have reported a dramatic reduction in menstrual bleeding with this approach. The IN spray is useful in a number of other situations as well. It can be given approximately 45 minutes before invasive dentistry or other out-patient procedures. In general, the resulting elevated levels of F VIII and vWf will last for 6-8 hours.

Oral contraceptive agents are also useful in reducing the severity of *menorrhagia*⁽¹²⁾ and are preferred by

some women and their physicians. As noted by Mannucci, it is common clinical experience that the continued use of oral contraceptives is very useful in reducing the severity of menorrhagia in women with vWD, even in those with Type 3 vWD.⁽¹²⁾

During pregnancy, level of vWf and F VIII rise in normal individuals and in those with Type 1 vWD⁽²⁰⁾ (although probably to a lesser extent⁽¹³⁾). Since the person with Type 1 vWD is able to produce structurally and functionally normal vWf, the rise seen in response to the hormonal changes of pregnancy often improves the woman's bleeding symptoms. Thus, the woman who has been having epistaxis and excessive bruising may note that these disappear during the last trimester of her pregnancy. In contrast, in women with Type 2A or 2B vWD, no improvement is seen.

Post-partum, there is a fall in vWf and F VIII levels over 7-10 days (and perhaps more rapidly in some), and post-partum hemorrhage may occur,^(12,21,22) necessitating treatment with DDAVP or a plasma-derived F VIII concentrate rich in the high molecular weight multimers of vWf.

For bleeding in the oropharynx, as well as for menorrhagia, an antifibrinolytic agent is often helpful. The tissues of the oral cavity are rich in fibrinolytic substances, and fibrinolytic activity has also been shown to increase during menstruation.^(12,23) Both ε-amino caproic acid (EACA) and tranexamic acid have proven useful; both of these agents are available in parenteral and oral formulations.

In women with Type 2 variants of vWD, as well as in the relatively rare cases of Type 3 vWD, one cannot rely on DDAVP. While DDAVP will effect a rapid release of vWf from endothelial storage sites, in Type 2 vWD the vWf released will be structurally and functionally abnormal and

generally will not improve hemostasis. (There may be *some* improvement following DDAVP in persons with Type 2A vWD; thus it may be worth a try in this variant.) In persons with Type 3 vWD, there is nothing in the storage sites to be released, and thus no improvement is seen. For excessive bleeding requiring treatment, or for surgical and post-operative coverage, one should use a plasma-derived F VIII concentrate rich in the higher molecular weight multimers of vWf (Table 5). While there is no generally accepted approach to monitoring,^(24,25) a recommendation appears in Table 6. It should be noted that, as of January, 1999, none of the plasma-derived F VIII concentrates marketed in the U.S. have a licensed indication for vWD *and* none of them have the vWf:RCo content on the label. Nonetheless, several of these products have clearly proven to be quite useful in preventing or controlling bleeding in persons with vWD who are unresponsive to DDAVP.

Other Hereditary Disorders of Blood Coagulation

Several other hereditary disorders of blood coagulation may be associated with menorrhagia and other bleeding symptoms in women (Table 7). These include isolated deficient-

Table 5 Management of Different Types and Subtypes of von Willebrand Disease

Type	Preferred Treatment	Alternative and Adjunctive Treatment
1	Desmopressin (DDAVP given IV or SQ, or Stimate nasal spray)	Antifibrinolytic agents, estrogens, oral agents contraceptive
2A	F VIII concentrates*	
2B	F VIII concentrates*	
2M	F VIII concentrates*	
2N	Desmopressin	
3	F VIII concentrates*	Platelet concentrates†

* One should use those plasma-derived F VIII concentrates which are rich in the higher molecular weight multimers of von Willebrand factor (examples of these are Centeon's Humate P, Alpha Therapeutics' Alphanate, Bayer Corporation's Koate HS)

† If bleeding persists despite replacement therapy, platelet concentrates may be useful, as platelet vWf plays an important role in establishing and maintaining primary hemostasis.⁽¹²⁾ Platelet vWf can be released from alpha granules directly to the site of vascular injury.

Table 6 General Guidelines for Treatment of von Willebrand Disease, Types 2 and 3

- A. For major surgery:
 - Maintain F VIII level and vWf:RCo level[†] ≥ 50% for 7-10 days (usually give a F VIII concentrate in a dosage of 20-40 u/Kg once or twice daily)
- B. For minor surgery:
 - Maintain F VIII level and vWf:RCo level[†] ≥ 50% for 1-3 days
 - Then maintain F VIII level > 20-30% for additional 4-7 days
- C. For dental extraction (permanent teeth):
 - Give a single large infusion to obtain peak of 50-60% F VIII (and vWf:RCo)
 - Also give an antifibrinolytic agent for 7 days, starting the day before extraction
- D. Intracerebral, gastrointestinal, or mucosal bleeding:
 - Maintain F VIII level and vWf:RCo⁺ level > 50% for 10 days (usually give F VIII concentrate in a dosage of 40 U/Kg once or twice daily)

Modified from Lusher JM: Treatment of Congenital Coagulopathies.⁽²⁵⁾

* While desmopressin is the treatment of choice for persons with Type 1 vWD, those with Types 2 and 3 should receive a plasma-derived F VIII concentrate rich in the hemostatically important high molecular weight multimers of vWf (ex: Humate P[®], Alphanate,[®] Koate HP[®]).

† At present (Jan., 1999), none of the F VIII concentrates marketed in the U.S. have vWf:RCo units on the label. Thus, dosage is calculated on basis of F VIII content. While many physicians obtain assays of RCo in patients' plasma, results are seldom available in time to adjust that day's dosage. Thus, most use F VIII assays and the patient's clinical condition as guides for follow-up dosing.

cies of F VIII or IX, F XI, the dysfibrinogenemias, and such rare disorders as afibrinogenemia, or deficiencies of F II, V, VII or X (see **Tables 8** and **9**). The latter have a frequency of 1-2 per million persons, and have usually become manifest in childhood. They are transmitted as autosomal recessive traits.

Low-Level Carriers of F VIII or F IX Deficiency. While severe hemophilia A or B is rare in females, many *carriers* of hemophilia A or B have subnormal levels of F VIII or F IX. As a result of lyonization, some may have very low levels (< 20%) and a bleeding tendency (**Table 10**). Carriers of F VIII deficiency with very low levels of

F VIII and bleeding should be treated with desmopressin (either parenterally or by IN spray). Those with very low levels of F IX and bleeding should be treated with a virally inactivated high purity plasma-derived F IX concentrate, or recombinant F IX.

F XI deficiency, which occurs most commonly (but not exclusively) in persons of Ashkenazi Jewish descent, may or may not be associated with a bleeding tendency. Certain families, with certain F XI genotypes, have bleeding problems and excessive bleeding with surgery, while other families do not.⁽²⁶⁾ While plasma-derived F XI concentrates are available in Europe, they are not in the U.S.; thus fresh frozen plasma (either donor retested or solvent-detergent treated) is generally used if treatment is judged indicated.

Hereditary disorders of blood platelets. While severe defects of platelet function such as Glanzmann's thrombasthenia and Bernard Soulier Syndrome are rare, and will have

become manifest and diagnosed early in life, others are somewhat more common, milder, and may be undiagnosed in women with excessive uterine bleeding. Storage pool defects and platelet release defects fall into this category. These disorders are generally manifest by mucous membrane bleeding and excessive bruising. If platelets are adequate in number, the bleeding time is prolonged, and other vWD screening tests are normal, one should consider the possibility of a platelet function defect (either hereditary or acquired). Platelet aggregation testing has been the main laboratory method used to diagnose and classify the hereditary platelet function defects.^(27, 28) Determination of storage pool organelles by transmission electron microscopy (TEM) and measurement of platelet nucleotides and serotonin (dense granules), or β -thromboglobulin and platelet factor 4 (α -granules) and their releasability can be used to confirm a suspected storage pool defect.⁽²⁷⁾

Acute bleeding episodes in hereditary platelet function defects (other than Glanzmann's thrombasthenia, or severe Bernard Soulier Syndrome) can usually be managed with desmopressin (DDAVP) infusions in a dosage of 0.3 μ g/Kg body weight. Adjunctive therapy with an antifibrinolytic agents such as ϵ -aminocaproic acid (Amicar[®]) may also be helpful in the case of mucous membrane bleeding.

Acquired Disorders of Hemostasis

A number of acquired disorders of hemostasis can also be manifest by excessive uterine bleeding, usually accompanied by other types of mucous membrane bleeding, excessive bruising and/or excessive bleeding following surgical procedures. The most common of these are idiopathic thrombocytopenic purpura (ITP), vitamin K deficiency states, drug-related thrombocytopenias, and platelet function defects. One often has a very good idea which of these is most likely following a pertinent history and physical examination and a few basic laboratory screening tests.

Table 7 Systemic Bleeding Disorders Associated with Excessive Uterine Bleeding

Hereditary Disorders of Hemostasis

- von Willebrand disease
- F VIII or F IX deficiency (low level "carriers" of hemophilia; rarely, homozygous F VIII or F IX deficiency state)
- F XI deficiency
- Other rare clotting factor deficiencies (ex: afibrinogenemia, F V, VII, X deficiencies)
- Dysfibrinogenemias
- Hyperfibrinolytic states
- ϵ_2 -antiplasmin deficiency
- PAI-1 deficiency
- Platelet function defects

Acquired Disorders of Hemostasis

- Autoimmune ITP (AITP)
- TTP, HELLP syndrome
- Drug-related thrombocytopenia
- HIV-related thrombocytopenia
- Platelet function defects
- Acquired F VIII inhibitor
- DIC
- Hepatocellular disease
- Vitamin K deficiency states
- Oral anticoagulants

Abbreviations: TTP, Thrombotic Thrombocytopenic Purpura; HELLP, Hemolysis, Elevated Liver Enzymes, Low Platelet Count

Table 9 Hereditary Disorders of Fibrinogen

- Afibrinogenemia and certain dysfibrinogenemias (e.g., fibrinogen Detroit) can result in menorrhagia
- PT, APTT, TT prolonged

Table 10 Bleeding Symptoms in Low-Level Carriers of F VIII or F IX Deficiency

- Menorrhagia
- Excessive bruising
- Miscarriages
- Excessive bleeding with procedures
 - D & C
 - C-section
 - Episiotomy
 - Epidural/spinal anesthesia
 - Amniocentesis
 - Invasive dentistry
 - Other surgery

Table 8. Rare Hereditary Disorders of Coagulation

Clotting Factor (F) Which is Deficient or Abnormal	Hemostatic Level	Half-Life in Circulation	Clinical States	Inheritance Pattern	Available Therapeutic Products	Dosage
F I (Fibrinogen)	50-70 mg/dl	3-4 days	- Afibrinogenemia	Autosomal recessive	Cryoprecipitate	1/5 units/10kg (usually one dose will suffice)
			- Hypofibrinogenemia - Dysfibrinogenemias (some assoc. with hemorrhage, some have no symptoms and some are associated with venous or arterial thrombosis)	Autosomal dominant Usually autosomal dominant	Cryoprecipitate Cryoprecipitate	1 unit/10kg (usually one dose)
F II (Prothrombin)	20 u/dl (20%)	60 hrs.	- Hypoprothrombinemia - Dysprothrombinemias	Autosomal recessive Autosomal recessive	Prothrombin complex concentrates (PCC) or FFP	15-20 ml FFP/kg initially then 15 ml/kg q 36-48 hrs
F V	0.25 u/ml (25%)	16 hrs.		Usually, Autosomal recessive (in some families, combined with F VIII)	FFP (less than 1-2 mos. old as F V is labile in frozen plasma)	20 ml/kg initially, then 10 ml/kg q 12-24 hrs.
F VII	0.10-0.20 u/ml	3-6 hrs.	Hemorrhagic symptoms highly variable, but may be severe	Autosomal recessive	FFP Plasma-derived F VII concentrate (not lic. in U.S.) rF VIIa (not lic. in U.S.) PCC (F VII content varies!)	FFP 10 ml/kg q 12 hr. 90 µg/kg q 2-3 hrs.
F X	25-30 u/dl	30 hrs.	F X deficiency Dysfunctional F X (acquired deficiency may be seen in amyloidosis)	Autosomal recessive Autosomal recessive	FFP Certain PCCs (assay their F X content, as this varies with the PCC and is not on label)	For minor bleeding, FFP 20 ml/kg initially, then 6 ml/kg q 12 hrs. For major bleeding, PCC
F XI	20 u/dl (20%)	2-1/2 - 3 days	Variable clinical manifestations. May be minimal, or more severe mucous membrane bleeding.	Autosomal recessive (most commonly seen in persons of Ashkenazi Jewish ancestry)	FFP (F XI concentrates are produced in Europe, not licensed in U.S.)	When necessary, 15-20 ml FFP/kg, then 7.5-10ml/kg q 12-24 hrs. Antifibrinolytic agents post-operatively if surg. involves mucosal surfaces.
F XII	None needed clinically		No excessive bleeding. May be a slight tendency to venous thrombosis.	Autosomal recessive	None needed	None
F XIII (Fibrin Stabilizing Factor)	0.02-0.03 u/ml (2-3%)	7-10 days	Intracranial hemorrhage, delayed bleeding after trauma, poor wound healing	Autosomal recessive (very rare)	Cryoprecipitate FFP (concentrates available in Europe)	1 unit / 10 kg every 7 days
Prékalikrein	None needed clinically		No excessive bleeding	Autosomal recessive or autosomal dominant	None needed	None
High Molecular Weight Kinogen	None needed clinically		No excessive bleeding	Autosomal recessive or autosomal dominant	None needed	None
α -2 antiplasmin		3 days	α -1 antiplasmin deficiency (results in excessive fibrinolysis), mucocutaneous bleeding, joint bleeding, delayed or recurrent bleeding	Autosomal recessive	Antifibrinolytic agents • ϵ -aminocaproic acid • Tranexamic acid	- 75 mg/kg q 6 hrs. - 25 mg/kg q 8 hrs.
Plasminogen activator inhibitor (PAI-1)			PAI-1 deficiency (results in excessive fibrinolysis; recurrent bleeding after surgery or trauma)	Autosomal recessive	Antifibrinolytic agents • ϵ -aminocaproic acid • Tranexamic acid	- 75 mg/kg q 6 hrs. - 25 mg/kg q 8 hrs.

Abbreviations: FI - factor I; FII = factor II; PCC = prothrombin complex concentrate; FFP = fresh frozen plasma; FV = factor V; FX = factor X; FXII = factor XII; FXIII = factor XIII

Idiopathic Thrombocytopenic Purpura. In adults (and in children > 10 years of age), ITP is usually of the autoimmune type (ATP). Autoimmune thrombocytopenic purpura is more common in females (being approximately 3 times more common than in men), often has an insidious onset, and is characterized by mucous membrane bleeding, petechiae and ecchymoses. Menorrhagia may be a major feature, with acute blood loss leading to syncope. Often one can elicit a family history of other autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, etc. In addition to thrombocytopenia, laboratory testing commonly shows other immunologic abnormalities such as a positive Coomb's test, positive antinuclear antibody (ANA), and reduced serum immunoglobulins.

Treatment is aimed at increasing the patient's platelet count to a safe range, and maintaining it. Corticosteroids (prednisone or methylprednisolone) are usually tried first; however, relatively few patients will have a complete remission. IVIG often produces a good response initially, but refractoriness ultimately develops in most. Splenectomy will effect a long-term remission in approximately 80% of patients.

Whether or not a woman with ATP has had a complete remission herself, her newborn infant may be born with moderate to severe thrombocytopenia; counts will rise by 6-8 weeks.

Drug-induced thrombocytopenia. Susceptible individuals can develop a syndrome resembling ITP after exposure to certain drugs. Such drugs (quinidine, quinine, sulfanilamides, chlorothiazide, valproic acid) bind to antidrug IgG on the surface of platelets. This results in platelet activation and in vivo aggregation.⁽²⁷⁾ In the case of heparin-associated thrombocytopenia (HAT), heparin forms a heparin antibody immune complex which binds to (and activates) platelets through the Fc receptors. HAT occurs in 1-3% of adults receiving heparin for a week or more. In 10-15% of those developing HAT, arterial or venous thromboses may occur. The latter may be fatal, or may result in amputation.⁽²⁹⁾ Several laboratory tests have been developed which can confirm the diagnosis of HAT.⁽²⁹⁾ Once a diagnosis of HAT is suspected, all sources of heparin should be stopped immediately.

Acquired platelet function disorders. A number of systemic disorders and drugs can induce platelet dysfunction, resulting in excessive bruising, mucous membrane-type bleeding, and excessive bleeding following surgery or trauma. Systemic disorders include uremia, liver disease and myeloproliferative disorders. Management consists of treatment of the underlying disorder. In each of these, desmopressin (DDAVP) may be helpful in decreasing the bleeding time and bleeding manifestations.

Certain classes of drugs (anti-inflammatory agents, certain antibiotics and anticoagulants) can interfere with platelet function. Acetylsalicylic acid (ASA), a cyclooxygenase inhibitor, interferes with the formation of thromboxane A₂ in the prostaglandin pathway of the platelet. The

effects of aspirin on a platelet are irreversible. Other non-steroidal antiinflammatory agents such as Ibuprofen, indomethacin and Naproxen are reversible inhibitors of platelet function. Clinical bleeding manifestations are seen most often if one of these drugs is taken by a person with an underlying bleeding disorder, such as vWD.

Acquired F VIII inhibitors. Although rare, acquired inhibitors against a clotting factor are almost always directed against F VIII. They are frequently associated with the sudden onset of life-threatening hemorrhagic complications; thus the appropriate diagnosis must be suspected and documented quickly. These F VIII autoantibodies may be seen in autoimmune disorders such as SLE and rheumatoid arthritis, and in postpartum women, as well as in a variety of other situations.⁽³⁰⁻³³⁾ They can occur at term or in the early postpartum period; in this situation, spontaneous disappearance of the inhibitor is not uncommon. Interestingly, in a study of 11 women who had postpartum acquired F VIII inhibitors, none recurred with subsequent pregnancies.⁽³³⁾

Acquired F VIII inhibitors often present dramatically, with the sudden appearance of rapidly expanding soft tissue hemorrhages, intractable epistaxis and/or gastrointestinal hemorrhage or uterine bleeding. Diagnostic puncture sites may lead to severe bleeding. The APTT will be prolonged and F VIII very low, often in the 3% range. A F VIII inhibitor assay will be positive. However, clinically it is important to note that the Bethesda assay may underestimate the in vivo potency of these inhibitors.⁽³⁴⁾ In contrast to F VIII inhibitors developing in hemophiliacs (which characteristically destroy F VIII in a linear, dose-dependent fashion), those developing in non-hemophiliacs demonstrate more complex reaction kinetics, with the antibody having decreased affinity for F VIII and incomplete inhibition of the F VIII activity. Thus, low levels of F VIII are detectable in the patient's plasma, despite the presence of a high concentration of autoantibody.⁽³⁵⁾

Treatment of acute bleeding is aimed at increasing the patient's circulating F VIII level. This can often be achieved by using porcine F VIII⁽³⁴⁾ (Hyate:C[®]) in a dosage of 50-100 F VIII U/dL, followed by intermittent bolus doses or continuous infusion, with dosage being guided by the patient's F VIII level. (A detailed schema for dosage calculation appears in reference #34.) Other therapeutic options which may be tried include high purity, plasma-derived or recombinant F VIII concentrates, and rF VIIa (Novo-Seven[®]). Additionally, in an attempt to eliminate or suppress the cell clone responsible for the synthesis of F VIII autoantibodies, Spero⁽³⁶⁾ and Green⁽³⁷⁾ and others have recommended the use of prednisone and cyclophosphamide.^(32, 37) However, as noted above, the F VIII autoantibodies seen in peripartum women often disappear spontaneously.

Vitamin K deficiency states. Vitamin K deficiency with overt bleeding may result from malabsorption syndromes (celiac disease, chronic diarrhea), coumarin overdosage, and with certain other drugs such as β -lactam antibiotics. The PT and APTT are often greatly prolonged, while the platelet count and thrombin time (TT) are normal. The PT is

usually more severely prolonged than is the APTT; the vitamin K dependent clotting factors (II, VII, IX and X) will be low. If the patient is bleeding, parenteral vitamin K (IM or SQ) should be given in a dosage of 10-20 mg. This should result in normalization of the PT and cessation of bleeding within 4-6 hours. In patients who are on coumadin and have severe bleeding, fresh frozen plasma should also be given. Bleeding in patients on oral anticoagulants is directly related to increases in the International Normalized Ratio (INR). Coumarin should be discontinued until the INR falls to the desired range (usually 2-3).

Summary

This brief review is meant to highlight the fact that a number of underlying systemic conditions can result in excessive uterine bleeding, and should be considered in one's differential diagnoses. While vWD is clearly the most common of these, others must be thought of as well. AITP most often develops in the second and third decades of life, is more common in women than in men, and may present with severe menorrhagia (generally with other mucous membrane bleeding, ecchymoses and petechiae) in women whose platelet counts are < 20,000/mm³. While acquired autoantibodies directed against F VIII are rare, they may occur in postpartum women, and in women with SLE or rheumatoid arthritis. Life-threatening hemorrhage may develop, necessitating rapid recognition of the proper diagnosis and institution of appropriate treatment.

As in other areas of medicine, a pertinent history, family history, and physical examination will be extremely helpful in making the diagnosis. Then a few well chosen laboratory tests will often document the suspected diagnosis so that the woman whose excessive uterine bleeding results from a systemic cause can be appropriately managed.

References

1. Lusher JM, Sarnaik S: Hematology. (Contempo Issue). JAMA 275:1814-1815,1996.
2. Rodeghiero F, Castaman G, Dini E: Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 69:454-459,1987.
3. Werner EJ, Broxson EH, Tucker EL, et al: Prevalence of von Willebrand disease in children: a multiethnic study. J Pediatr 123:893-898,1993.
4. Ewenstein BM: von Willebrand's disease. Ann Rev Med 48:525-542,1997.
5. von Willebrand E: Hereditar pseudo-hemofili. Finska Lak Handl 68:87,1926.
6. Ruggeri ZM: Pathogenesis and classification of von Willebrand disease. Haemostasis 24:264-275,1994.
7. Meyer D, Girma JP: von Willebrand factor: structure and function. Thromb Haemost 70:99,1993.
8. Jorieux S, Gaucher C, Goudemand J, Mazurier C: A novel mutation in the D3 domain of von Willebrand factor markedly decreases its ability to bind Factor VIII and affects its multimerization. Blood 92:4663-4670,1998.
9. Sadler JE: A revised classification of von Willebrand disease. Thromb Haemost 71:520-525,1994.
10. Montgomery RR, Gill JC, Scott JP: Hemophilia and von

Willebrand disease. In: Nathan DG, Orkin SH, eds. Nathan and Oski's Hematology of Infancy of Childhood. 5th Ed., Philadelphia, W.B. Saunders, 1998, pp. 1631-1659.

11. Mannucci PM: Treatment of von Willebrand disease. J Intern Med 242 (suppl. 740):129-132, 1997.
12. Mannucci PM: Treatment of von Willebrand disease. Haemophilia 4:661-664,1998.
13. Kouides PA: Females with von Willebrand disease: 72 years as the silent majority. Haemophilia 4:665-676,1998.
14. Montgomery RR, Coller BS: von Willebrand disease. In: Colman RW, Hirsh J, Marder VJ, et al, Eds. Hemostasis and Thrombosis: Basic Principles and Practice. Philadelphia, JB Lippincott, 1994, pp. 134-168.
15. Federici AB: Diagnosis of von Willebrand disease. Haemophilia 4:654-660,1998.
16. Lethagen S, Ragnarson Tennvall G: Self-treatment with desmopressin intranasal spray in patients with bleeding disorders: effect on bleeding symptoms and socioeconomic factors. Ann Hematol 66:257-260,1993.
17. Kobrinsky N, Goldsmith J: Efficacy of Stimate (desmopressin acetate) nasal spray, 1.5 ng/mL, for the treatment of menorrhagia in women with inherited bleeding disorders. Blood 90:3186 (abstract), 1997.
18. Mannucci PM, Bettega D, Cattaneo M: Consistency of responses to repeated DDAVP infusions in patients with von Willebrand disease and haemophilia A. Br J Haematol 82:87-93,1992.
19. Lusher JM: Response to 1-deamino-8D-arginine vasopressin (DDAVP) in von Willebrand disease. Haemostasis 24:276-284,1994.
20. Conti M, Mari D, Conti E, et al: Pregnancy in women with different types of von Willebrand disease. Obstet Gynecol 68:282-285,1986.
21. Krishnamurthy M, Miotti AB: von Willebrand's disease and pregnancy. Obstet Gynecol 49:244-247,1977.
22. Greer IA, Lowe GD, Walker JJ, Forbes CD: Hemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. Br J Obstet Gynaecol 98:909-918,1991.
23. Cederbald G, Hahn L, Korsan-Bengtson K, et al: Variations in blood coagulation, fibrinolysis, platelet function and various plasma proteins during the menstrual cycle. Haemostasis 6:294-302, 1977.
24. Lusher JM: Clinical guidelines for treating von Willebrand disease patients who are not candidates for DDAVP - a survey of European physicians. Haemophilia 4 (suppl. 3):11-14,1998.
25. Lusher JM: Treatment of congenital coagulopathies. In: (Mintz PD, ed.), Transfusion Therapy: Clinical Principles and Practice, AABB Press, Bethesda, 1999, pp. 97-128.
26. Smith JK: Factor XI deficiency and its management. Haemophilia 2:128-136,1996.
27. Hathaway WE & Goodnight SH, Jr: Disorders of Hemostasis and Thrombosis. A Clinical Guide. McGraw Hill, Inc., New York, 1993, Chapter 10.
28. Rao AK: Congenital disorders of platelet function. Hematol Oncol Clin NA 4:65, 1990.
29. Hathaway WE & Goodnight SH, Jr: Disorders of Hemostasis and Thrombosis. A Clinical Guide. McGraw Hill, Inc., New York, 1993, Chapter 46.
30. Green D, Lechner K: A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. Thromb Haemost 45:200-23, 1981.

31. Hultin MB: Acquired inhibitors in malignant and nonmalignant states. *Am J Med* 91 (suppl. 5A):9-13,1991.
32. Cohen A and Kessler CM: Autoantibodies against clotting factors. *Bailliere's Haematology*.
33. Coller BS, Hultin MK, Hoyer LW, et al: Normal pregnancy in a patient with a prior postpartum factor VIII inhibitor: observations on pathogenesis and prognosis. *Blood* 58:619-624,1981.
34. Kasper CK: Raising Factor VIII levels in patients with acquired factor VIII inhibitors. In: (Kessler CK, ed.), *Acquired Hemophilia*, second edition. Excerpta Medica, Inc., Amsterdam, 1995, pp. 41-69.
35. Gawryl MS, Hoyer LW: Inactivation of factor VIII coagulant activity by two different types of human antibodies. *Blood* 60:1103-1109, 1982.
36. Spero JA, Lewis JH, Hasiba U: Corticosteroid therapy for acquired F VIII:C inhibitors. *Br J Haematol* 48:635-642,1981.
37. Green D: Cytotoxic suppression of acquired Factor VIII:C inhibitors. *Am J Med* 91 (suppl. 5A):14-19,1991.