
BLEEDING DISORDERS IN WOMEN

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Bleeding issues specific to women and adolescent females are common across the world. These issues relate particularly to menses, pregnancy and childbirth. In this article diagnosis and treatment of females with bleeding disorders in various stages of life will be discussed.

Bleeding Disorders in Women

Women with a variety of bleeding disorders can have symptoms that result in significant morbidity and impact their quality of life.¹ Increased absence from school or work and decreased quality of life have been documented.² Acute and chronic effects from iron deficiency anemia are seen. Iron deficiency is a problem in menstruating females worldwide. A study in Bursa, Turkey found anemia in 32.8% of 530 women ages 15-49 randomly selected from 6506 women.³ In women with bleeding disorders the prevalence is likely higher. In addition life threatening hemorrhage such as severe postpartum hemorrhage or rupture of hemorrhagic ovarian cysts can occur.

Von Willebrand disease (VWD) is the most common inherited bleeding disorder. Von Willebrand factor (VWF) serves as the initial link between the platelet and the subendothelium. Because of this role bleeding symptoms tend to be platelet-like and mucosal bleeding predominates. VWF also stabilizes FVIII, and in patient with more severe forms of VWD can also have symptoms related to a low FVIII, including joint bleeding in those severely affected.

Inherited platelet disorders are also associated with gynecologic and obstetric bleeding.⁴ In some populations may be more common than VWD. This is true in African Americans who have higher

plasma VWF levels than Caucasians.^{6,7} Carriers of factor VIII and factor IX deficiency and patients with more rare bleeding disorders also have issues with gynecologic bleeding. Deficiencies of factor XI, VII or X are noted for mucosal bleeding, as well as other bleeding symptoms.⁵

Manifestations of Bleeding Disorders in Women

Bleeding from the reproductive tract occurs normally in females but for those with underlying bleeding disorders this presents particular challenges. This begins with menarche. Menorrhagia from menarche is frequently seen in females with bleeding disorders.⁸ Menorrhagia is generally defined as greater than 80 cc of blood loss/cycle which is the amount of blood loss that would result in iron deficiency anemia. The following symptoms and findings are associated with menorrhagia and include: soaking through a pad or tampon within 1 hour, soaking through bed clothes, below normal ferritin, anemia, and a pictorial blood assessment chart score of greater than 100.⁹ The pictorial chart was developed as a way to assess menstrual blood loss without collecting menstrual pads and tampons.¹⁰ Bleeding challenges may increase with peri-menopausal related bleeding.

In a review of studies by a panel appointed by the National Heart, Lung and Blood Institute of the NIH in the U.S., there was a prevalence of menorrhagia in 32 – 100% of women with VWD.¹¹ This and additional bleeding symptoms are shown in Table 1.

Table 1. Prevalence of Bleeding Symptoms in Females with VWD

Menorrhagia	32-100%
Epistaxis	38%-62%
Bleeding after Dental Extraction	28%-52%
Ecchymoses	49%-52%
Bleeding from Minor Cuts or Abrasions	36%
Gingival Bleeding	26%-35%
Hemarthrosis	20%-28%
GI Bleeding	14%

Carriers of hemophilia A (FVIII) or B (FIX) deficiency can have symptoms depending on their baseline level of clotting factor activity. Only one X chromosome is active in each factor VIII or IX producing cell. Since this is random there is a Gaussian distribution of factor levels and some carriers have very low factor levels. In a study of mothers of sons with hemophilia in the Netherlands they found that women with levels up to 60% manifest increased bleeding symptoms and menorrhagia was the most common symptom.¹²

Table 2. Bleeding Disorders in Women with Menorrhagia

VWD	5%-20%
Platelet Dysfunction	<1%-47%
Factor XI Deficiency	<1%-4%
Hemophilia Carriage	<1%-4%
Rare Factor Deficiencies	<1%

Menorrhagia as a Presenting Symptom

A number of studies have evaluated the presence of underlying bleeding disorders in women with menorrhagia. Find vary among studies and the ranges are shown in Table 2.⁸

Bleeding with Childbirth

Postpartum hemorrhage is a common complication of delivery, and this is usually not due to an underlying bleeding disorder. However women with bleeding disorders are more likely to have

bleeding complications during pregnancy, with delivery and postpartum.¹³ Hemorrhage at the time of delivery is usually due to lack of uterine contraction. Women with significant bleeding disorders may not have excessive bleeding from the uterus, but may bleed extensively from surgical wounds, either cesarean section or episiotomy. Perineal hematomas are a common complication of delivery in women with bleeding disorders.¹⁴

Specific factor deficiencies can manifest different issues in pregnancy. Women with severe FXIII or fibrinogen deficiencies have problems with pregnancy loss and need supplementation to carry a pregnancy to term. Other bleeding disorders are not clearly associated with an increased risk of miscarriage. VWF, FVIII and fibrinogen all increase markedly during pregnancy. Most women with mild VWD and carriers of FVIII normalize their level during pregnancy.¹⁵ A recent study following women with type 1 VWD prospectively documented normalization of levels with pregnancy, but with wide variability in the magnitude of increase.¹⁶ This demonstrated a need to check levels early in the 3rd trimester to document adequacy for delivery. VWF, FVIII and fibrinogen levels fall postpartum, approaching baseline values by 6 weeks. Because of this women may not have excessive bleeding at the time of delivery but may have delayed postpartum bleeding.

Table 3. Findings to Prompt an Evaluation for a Bleeding Disorder

Menorrhagia since menarche
Family history of a bleeding disorder
Recurrent epistaxis requiring medical attention
Notable bruising without injury (> 2 cm)
Bleeding from trivial cuts for > 5 minutes
Bleeding from oral cavity or GI bleeding without obvious cause
Prolonged or unexpected bleeding after dental extraction
Unexpected postoperative bleeding
Hemorrhagic ovarian cysts
Hemorrhage requiring transfusion
Postpartum hemorrhage, especially delayed
Failure of response to conventional management of menorrhagia

Diagnosis of Bleeding Disorders in Women

When should a women who be evaluated for an underlying bleeding disorders? In a woman who presents with menorrhagia, findings in the history which should prompt an evaluation include those listed in Table 3.⁹

Diagnostic Approach for Women with Bleeding Symptoms

A diagnostic approach should begin with a complete blood count to evaluate for anemia or thrombocytopenia. Iron stores should be assessed, usually with a serum ferritin. A peripheral smear should be examined to evaluate platelet morphology. A baseline prothrombin time, aPTT and thrombin time should be drawn. Further evaluation should be guided by patient and family history and screening laboratory results. In mild VWD and in some type 2 VWD the FVIII will be high enough such that the aPTT may not be prolonged; thus a normal aPTT does not rule out VWD. In patients with mucosal bleeding symptoms who do not have VWD, platelet function studies should be performed. In patients with a prolonged prothrombin time and/or aPTT factor analyses should be performed as indicated. In patients with symptoms and family history consistent with autosomal recessive inheritance rare factor, alpha₂antiplasmin, FXIII and plasminogen activator inhibitor-1 deficiencies should be considered.

Currently used hormonal contraceptives do not significantly increase VWF or FVIII levels and do not need to be stopped for laboratory testing.¹⁷ They do blunt the cyclical variation in levels seen in women not on hormonal treatment. In such women, levels are lowest early in the menstrual cycle and in women who have borderline levels, repeat testing at that time may be warranted. Stress, exercise and inflammation increase VWF, FVIII and fibrinogen levels. Care should be taken to try to minimize these variables when undertaking laboratory assessment.¹⁸

Treatment of Menorrhagia in Women with Bleeding Disorders

Menorrhagia in women with underlying bleeding disorders often responds to treatments used for menorrhagia in general. This includes hormonal contraceptives or antifibrinolytic therapy. Women with underlying bleeding disorders may respond well to several months of continuous hormonal contraceptives, although they may have break-

through bleeding earlier than is usually seen. The involvement of a gynecologist with experience in treating women with bleeding disorders is beneficial. The progesterone coated IUD is another good alternative as it has been shown to decrease menstrual blood loss in women with underlying bleeding disorders.¹⁹ In women who have finished their child-bearing, uterine ablation is an option and is generally considered prior to hysterectomy. In women who are carriers of hemophilia A or have VWD, desmopressin is an option, although it is generally not as efficacious as tranexamic acid in this setting.²⁰ Patients with more severe disorders may require factor infusions during menses or a combination of therapies.

Managing Pregnancy in Women with Bleeding Disorders

Ideally women with bleeding disorders will have a planned pregnancy with collaborative care from a hematologist and a maternal fetal medicine specialist. In women with Type 1 VWD, levels should be checked at the beginning of pregnancy and around 36 weeks; the latter to ensure that normalization of values has occurred. In women whose values normalize prior to delivery, epidural anesthesia and cesarean section can be performed without treatment, but providers and the patient should be warned about the risk of postpartum hemorrhage when the levels begin to fall. A similar approach is taken for the women who has a low factor VIII level as a carrier of hemophilia A. However, additional considerations will be taken depending on whether she is delivering an affected male infant. Women with Type 1 VWD or mild FVIII deficiency may bleed more from a miscarriage early in pregnancy than with deliveries later because their levels have not yet normalized.

Women with other factor deficiencies, including carriers of hemophilia B, or platelet disorders will require a specific approach depending on the deficiency. Women who are carriers of hemophilia B and who have low FIX levels are at risk of bleeding complications throughout pregnancy and may require factor replacement. In general levels are targeted to above 50% for the delivery and continued after delivery for a length of time depending on the mode of delivery.¹ In women with mild platelet function disorders, the use of desmopressin and antifibrinolytic therapy may limit the need for platelet transfusion.

Summary

Bleeding disorders in women result in significant complications and worse quality of life. Appropriate diagnosis and treatment are key to improving outcomes in these patients.

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