NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

Women with Bleeding Disorders

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The original chapter on Women with Bleeding Disorders for this manual was written by the late Renee Paper, RN, CCRN who was a woman with a bleeding disorder and a tireless pioneer advocate for women who bleed.

Inherited bleeding disorders affect females as well as males. Pathological bleeding in women has the potential to affect the lives of all of us, since everyone has a mother, sister, wife, or daughter, and female friends and one or more of them might have an inherited bleeding disorder. Many healthcare providers are not aware of the prevalence of bleeding disorders among females and may believe that genetic causes of prolonged bleeding occur only in men. However, women can be affected by several different inherited bleeding disorders such as von Willebrand disease (VWD); qualitative platelet defects, Hemophilia A, B or C; and other rarer clotting factor deficiencies; as well as disorders involving the fibrinolytic system.

Males and females with inherited bleeding disorders have many symptoms in common. Mouth and nose bleeds, easy bruising, and prolonged bleeding with surgeries and trauma occur in both genders. However, females can experience heavy menstrual bleeding (HMB). HMB is frequently reported by women with bleeding disorders and can lead to pain, chronic anemia, hospitalization, blood transfusions, school and work absences, limitations in daily activities, and reduced quality of life. Other types of bleeding that are specific to females include hemorrhage during pregnancy and childbirth. The risk of life-threatening hemorrhage and hysterectomy in women with inherited bleeding disorders appears to be much greater than that of the general population. (1)

The prevalence of bleeding disorders in females is not known. However, von Willebrand Disease (VWD), the most common bleeding disorder in humans, may affect between 1% and 3% of the population.(2) Among women seeking medical care for menorrhagia, the incidence of VWD or another bleeding disorder may be as high as 10- 20%. (3)

This chapter will highlight the common inherited bleeding disorders that may affect females and the bleeding complications that they may experience. We will also give an overview of potential treatments available for the treatment of bleeding disorders in women.

DIAGNOSIS OF BLEEDING DISORDERS IN WOMEN

Women are most commonly evaluated for a bleeding disorder due to having a family history of a bleeding disorder, a personal history of bleeding symptoms, or having elevated screening laboratory results prior to a surgery or procedure.

Evaluation for an inherited bleeding disorder is most effectively performed by a knowledgeable hematology team. A federally funded specialty hemophilia treatment center (HTC) will have experienced doctors, nurses, social workers and physical therapists to provide a thorough evaluation. Additionally, most HTCs will have availability of a specialty coagulation laboratory to provide accurate testing.

Evaluation for a bleeding disorder involves taking a detailed family history with a pedigree of bleeding symptoms/ diagnoses, taking a personal bleeding history using a validated bleeding assessment tool (BAT), physical examination,

and laboratory testing (4). A pictorial bleeding assessment chart (PBAC) can be helpful in quantifying menstrual blood loss. Initial laboratory testing often includes a complete blood count, PT, aPTT, Thrombin time, and Fibrinogen. Testing for von Willebrand disease includes: Factor VIII activity, vWF antigen level, vWF activity level (or Ristocetin Co-Factor). A platelet function analyzer- 100 (PFA- 100) can provide additional information in the initial testing phase. If more testing is needed to fully characterize the bleeding disorder platelet aggregation testing is performed. Additional testing for rare bleeding disorders often requires sending specimens to an outside laboratory.

Laboratory measures for common bleeding disorders exhibit a high degree of variability over time. (3) Factor levels may be affected by things like stress, illness, hormones and medications, so it is recommended that people be tested more than once for a definitive diagnosis. (3) Many experts recommend timing at least one episode of blood testing to coincide with the beginning of menstrual bleeding, in order to capture the lowest levels of von Willebrand factor and Factor VIII.

Community physicians may know little about testing for bleeding disorders. Blood specimens collected for coagulation testing must be handled with great care or the specimen degrades, making a diagnosis difficult. When specimens must be shipped to an outside laboratory, there is an additional opportunity for mishandling, leading to degradation of the specimens. Interpretation of testing for inherited bleeding disorders is challenging, so it is recommended that tests are performed and interpreted by an experienced hematology provider.

TYPES OF BLEEDING DISORDERS IN WOMEN

Von Willebrand Disease

VWD is the most common inherited bleeding disorder. It affects men and women equally. VWD follows and autosomal dominant inheritance pattern. Bleeding in VWD is predominantly mucocutaneous, and symptoms of nose bleeding, mouth bleeding and easy bruising are common. These can be dismissed by medical providers because they are difficult to quantify. Often evaluation for bleeding disorders is delayed until adolescence when HMB occurs in the young woman.

Women with VWD often have both prolonged and profuse menstrual bleeding. Menses may continue for 10-14 days, instead of the average 5-day cycle experienced by most women (5). Changing pads or tampons as often as every hour is a common experience for the woman with VWD. Using double protection and flooding of menstrual blood through the protection and onto clothing or bedding is often reported.

While studies suggest that as many as 15-20% of women seeking care for HMB may have VWD, a 2002 CDC study found that only 4% of gynecologists responding to the survey would consider VWD a cause of the heaving bleeding (6). Subsequent recommendations published in the American Journal of Obstetrics and Gynecology encourage providers to suspect VWD when evaluating women for HMB (7).

Women with VWD can also have post-surgical bleeding as well as bleeding with injury. There may be increased incidence of gastrointestinal bleeding in some forms of VWD (8).

*See Chapter on VWD for more information.

Carriers of Hemophilia with Bleeding Symptoms

Hemophilia A and B are x- linked disorders, primarily affecting males, however women who are genetic carriers of hemophilia A or B have one gene affected by hemophilia and one that is unaffected. Often hemophilia carriers are found to produce approximately half of the normal Factor VIII or IX levels as non- carriers. There is a wide range of factor levels found in carriers of Hemophilia A and B as well as a wide variety of bleeding symptoms.

A woman whose father has hemophilia A or B is considered an "obligate carrier", since the only x chromosome that can be contributed by the father is affected with the disorder. If a woman has a son with hemophilia and any other maternal relative affected by the condition, she is presumed to be a carrier. Additionally, women are found to be a carrier of hemophilia after giving birth to a son with hemophilia and having laboratory testing performed.

A normal Factor VIII or IX level does not rule out the possibility of a female being a carrier. Genetic testing remains the gold standard for carrier determination and should be pursued so that the correct determination of carrier status can be made (2).

A woman may be born into a family with a long history of hemophilia or may be surprised to discover that she is affected by a new genetic mutation. This may occur in up to 30% of new cases of hemophilia. In any case, female carriers of hemophilia should be tested so that their baseline factor level is known.

Factor VIII or IX levels in female carriers have been reported to range from 4% to 80%, with levels of 40% to 60% being common. While hematologists previously felt confident that excessive bleeding would not occur in those whose factor levels were at least 25- 30%, one study gave evidence that increased bleeding occurred in carriers with factor levels up to 60% as compared to controls (9). Female carriers who have lower than normal factor levels should be considered persons with mild hemophilia.

As women with hemophilia, treatment for bleeding episodes should be offered and care should be on parity with the treatment offered males with the same disorder. The labeling with a diagnostic name is much discussed today among women in this community. The name carrier, symptomatic carrier, hemophiliac, or carrier with symptoms seems to be a personal choice and should be treated as such. Insurance, coding and billing may come in to play depending on the diagnostic code or label used.

Women with more Severe Hemophilia

Although rare, cases of severe (<1% Factor level) and moderate (1-5 % factor level) hemophilia A and B are found in women. The cases usually fall into one of two categories. Either the woman inherited a hemophilia gene from both her father with hemophilia and her mother who is a carrier, or she is a genotypic carrier who has extreme lyonization of the hemophilia gene, causing the normal gene for production of factor VIII or Factor IX to be "turned off". Women who have moderate to severe hemophilia will have bleeding like that of males with the same severity of hemophilia, with the added feature of gynecologic and obstetric problems that make clinical management more challenging.

Rare Bleeding Disorders in Women

Factor XI deficiency is a very rare bleeding disorder. Sometimes called Hemophilia C, it affects approximately 1 in 100,000 people in the United States. It follows an autosomal dominant inheritance pattern, meaning that males and females are equally affected.

Persons with Ashkenazi Jewish heritage are found to be more frequently affected, leading to a higher incidence of Factor XI deficiency in areas with large populations from eastern European countries or those with Israeli heritage. Increasingly Factor XI deficiency is being found in persons from many ethnic groups, as well as in those with no family history of bleeding (10).

Little is knowns about Factor XI deficiency. For reasons that are not well understood, bleeding symptoms do not seem to be directly related to the level of FXI found in the blood, making it difficult to predict severity of bleeding. Prolonged bleeding may occur with surgeries, dental extractions and injury, as well as gynecological bleeding like what occurs with von Willebrand disease.

Other rare factor deficiencies may be found in women. Factor V, Factor VII, Factor X, Factor XIII and combined Factor V and VIII deficiencies all may produce mild to severe bleeding symptoms. Afibrinogenemia (also known as Factor I deficiency) may produce severe bleeding symptoms. Dysfibrogenemia is diagnosed when fibrinogen is found in lower quantity as well as abnormal quality, leading to prolonged bleeding.

Platelet dysfunction syndromes may be found in women. These occur when platelets are present in adequate quantity but the platelets do not function properly. Moderate – to -severe bleeding can be seen in conditions such as Bernard-Soulier syndrome and Glanzmann's Thrombasthenia. Milder bleeding symptoms are found in platelet storage pool or platelet aggregation disorders. All of the platelet disorders can lead to bleeding symptoms similar to those found in VWD.

Disorders of hyperfibrinolysis, or excessive early breakdown of blood clots can lead to bleeding symptoms in men and women. One such disorder is called plasminogen activator inhibitor type I (PAI-I) deficiency. The incidence of this disorder is unknown, but it appears to affect men and women equally, with symptoms similar to those of von Willebrand disease.

TREATMENT FOR GYNECOLOGIC AND OBSTETRIC BLEEDING

The non- gynecologic symptoms of bleeding in women, such as bruising, epistaxis, joint and soft-tissue bleeding, as well as postoperative and post-dental bleeding, are addressed elsewhere in this manual and will not be repeated here. The bleeding symptoms specific to women involve the reproductive tract and include HMB, dysmenorrhea, painful ovulation, postpartum bleeding and hemorrhage following abortion (spontaneous or therapeutic).

Heavy Menstrual Bleeding (HMB)

HMB is defined as menstrual bleeding in excess of 80 mls per cycle. This is often difficult to quantify. The gold standard for measurement of menstrual fluid loss in a research setting is the alkaline hematin technique. While reasonably accurate, this method requires that all feminine hygiene products from a menstrual cycle be collected and provided to the laboratory for testing, making it impractical for routine clinical assessment of bleeding. Pictorial charts (PBAC) have been developed and validated as useful in screening for menorrhagia, with a reported predictive value of 75-85%. When using the chart feminine hygiene product use is recorded, and scored depending on the saturation level. Points are given with a total score of 100 or more being correlated with a diagnosis of menorrhagia (3).

Another definition of HMB is "excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life". When accepting this definition clinicians aim to improve quality of life for the affected woman.

Treatment for HMB may involve hormone therapies, desmopressin acetate, antifibrinolytic agents and/or replacement clotting factor. Often combination therapy is required to adequately control HMB in a woman with a bleeding disorder. Unfortunately trial and error are often used to arrive at the optimal therapeutic regimen.

Estrogen raises the level of clotting factors II, VII, VIII, X and von Willebrand factor (VWF). Estrogen can be administered conveniently in the form of oral contraceptive pills and patches. Hormone therapy can be helpful in treating HMB in all bleeding disorders due to its ability to regulate the menstrual cycle and decrease the duration of the menstrual bleeding. Other agents such as the hormone releasing intrauterine device (Mirena®, Bayer Healthcare) and progestin injections (Depo-provera injection®, Pfizer) can also be effective treatments.

Desmopressin acetate (DDAVP) may help raise circulating levels of Factor VIII and VWF in many women with mild to moderate hemophilia A, mild type I von Willebrand disease, and in some mild platelet function disorders. Testing should be performed prior to using DDAVP to insure that the factor levels will increase with use. Currently Stimate® (DDAVP in nasal spray form) (CSL Behring) is not available due to manufacturer recall. However, DDAVP remains available in subcutaneous and intravenous forms. Caution must be taken when using DDAVP in any form to avoid excessive fluid intake after its use as hyponatremia can develop. Other side effects of DDAVP can include headache, increased blood pressure and facial flushing, most often of short duration. Many women find that using DDAVP for the first 2-3 days of their menstrual period reduces duration and quantity of blood loss.

Antifibrinolytiic medications are often used along with other therapies to help slow the breakdown of blood clots. They are especially effective for mucous membrane bleeding, including mouth and nose bleeding, as well as in treating HMB. The two products most often used are aminocaproic acid (Amicar) and tranexamic acid (Lysteda).

Women who have von Willebrand disease or another factor deficiency may need to use factor replacement products to treat bleeding episodes. Those with factor deficiencies for which virally attenuated clotting factor replacement products are available, should be prescribed the clotting factor. When no virally attenuated products are available, cryoprecipitate or fresh-frozen plasma (FFP) may be used. Those who use factor frequently should be given the opportunity to learn self-infusion. Self-infusion allows a greater degree of autonomy in managing the bleeding disorder and results in better quality of life.

Surgical intervention in the form of endometrial ablation or hysterectomy should only be considered after the woman has failed non-surgical therapies for treatment of HMB. Endometrial ablation may be a safer procedure for the treatment of HMB because it is not as invasive as hysterectomy. However, it is not always effective in long-term control of heavy menstrual bleeding (11). Since both hysterectomy and endometrial ablation will render the woman unable to carry a pregnancy, the woman's reproductive choices should be strongly considered before advising surgery.

DYSMENORRHEA

Dysmenorrhea is defined as painful menstruation. Women with bleeding disorders who experience dysmenorrhea may actually have endometriosis (5). Endometriosis is a condition in which endometrial tissue has migrated outside of the uterus and can be particularly problematic in women with bleeding disorders. The extra endometrial tissue will bleed, sometimes excessively, each month with menstruation, leading to free blood in the abdomen. Free blood in the abdomen can cause severe pain.

Mittelschmerz or pain at ovulation (mid-cycle) may indicate the presence of ovarian cysts. For a woman with a bleeding disorder, and ovarian cyst can be quite painful and if the cyst ruptures, excessive bleeding may occur within the abdominal cavity. It is thought that women with bleeding disorders have a greater incidence of ovarian cysts (5).

Treatment of menstrual pain often involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), which may actually worsen the condition. Many NSAIDs cause platelet dysfunction, and this may make bleeding symptoms worse. Medications such as choline magnesium trisalicylate (Trilisate) or celecoxib (Celebrex) may be helpful due to their lesser effect on platelet function.

Obstetric Complications

Women with bleeding disorders should be able to conceive and carry a pregnancy to term and experience a safe delivery. The exception to this rule may be found in women with fibrinogen deficiency and/ or Factor XIII deficiency. Reports from the last 20 years have suggested an increase in miscarriage and placental abruption resulting in fetal loss

or premature delivery in these disorders (5). In any case, managing the pregnancy of a woman with a bleeding disorder requires a multidisciplinary team that will consider the risk of bleeding for the mother and baby; what prenatal and early diagnostic options are available for the infant; and medical management of the pregnancy, delivery and postpartum period. Women at risk for severe bleeding should be referred for prenatal care and delivery to a center where, in addition to specialists in high-risk obstetrics there is a hematologist with expertise in hemostasis. Laboratory, pharmacy and blood bank support is also required. Prior to delivery women with bleeding disorders should also have the opportunity to meet with an anesthetist. Factor levels should be at least 50% at time of delivery to consider regional anesthesia. (5) Ideally many of these discussions will begin during preconception counseling so that the woman with a bleeding disorder and her partner can make informed decisions about reproduction.

Multiple methods exist for the definitive pre-natal diagnosis of hemophilia. Unfortunately these methods are all invasive and may place the woman at risk for excessive bleeding. Amniocentesis, chorionic villus sampling and cordocentesis must all be undertaken with awareness of the risk of bleeding and/or miscarriage (12). Conditions such as von Willebrand disease and platelet dysfunction are not as easily diagnosed before the birth of the infant.

Fetal sex determination can be useful in the management of pregnancies at risk for hemophilia A or B. The discovery that a fetus is female may be reassuring to the parents who will know that invasive prenatal testing is not required. When a male child is expected, the delivery can be planned to avoid instrumental deliveries and trauma to the infant during the birth process.

Pre-implantation genetic diagnosis is a high-tech technique that allows embryos created using in-vitro fertilization (IVF) to be tested to determine which are affected by a genetic condition like hemophilia. The unaffected embryos are then implanted, avoiding the difficult decision of whether to terminate a pregnancy because of hemophilia. There have been reports that some women who are carriers of hemophilia have used this method of reproduction to ensure that they will have a child that is not affected with the condition. IVF is an expensive therapy, so the costs of the procedures need to be considered when planning its application.

Since normal pregnancy is accompanied by increased levels of several clotting factors and a decrease in fibrinolytic activity, pregnancy is considered a hypercoagulable state. This means that many women are at risk for too much clotting while pregnant. Women with bleeding disorders will often have improved hemostasis and fewer bleeding symptoms while pregnant. However, some women with bleeding disorders will not be able to attain the same levels of clotting factors that are found in women who do not have bleeding disorders and thus will still be at risk for bleeding during pregnancy. These women will require treatment to prevent bleeding and to maintain the pregnancy.

Blood factor level testing at different times during the pregnancy will help the medical team caring for these women to determine the need for treatment to prevent bleeding.

Advice about method of delivery for women with bleeding disorders varies. Many providers advise vaginal delivery, with the understanding that any evidence of fetal distress should be managed by cesarean section. Some obstetricians recommend that planned cesarean section is the preferred method of delivery if moderate to severe hemophilia is suspected. All of those knowledgeable about bleeding disorder strongly insist that instrumented delivery and the use of suction should be avoided.

Post-partum hemorrhage occurs more frequently in women with bleeding disorders than those who are unaffected. Some studies suggest that the incidence of post-partum hemorrhage in women with bleeding disorders may be as high as 22% compared to 5% in the general population. Postpartum bleeding in women with inherited bleeding disorders may occur 3- 15 days or more after vaginal delivery (13). Clotting factors, which are elevated during pregnancy return to

pre-pregnancy levels within 21 days of delivery (5). A plan for management of secondary postpartum hemorrhage should be developed for the woman with a bleeding disorder.

Infertility is defined as difficulty becoming pregnant. Many women with bleeding disorders report having trouble getting pregnant. There is little research to report the incidence or cause of infertility in women with bleeding disorders. In addition, many women with bleeding disorders report that they have experienced spontaneous abortion (miscarriage). It is not known whether this can be attributed to their bleeding disorder. It is known that women with bleeding disorders who have miscarriages are at risk for serious bleeding due to the precipitous drop in factor levels that occur soon after the loss of a pregnancy. Good hematologic care is advised during and after spontaneous or therapeutic abortion.

Psychosocial Issues

It is usually said that men have hemophilia and women are carriers. This terminology is significant. Women are often viewed as a passive vehicle for the transmission of an inherited bleeding disorder, which often limits their ability to access healthcare and to have their diagnosis and bleeding symptoms acknowledged within healthcare systems (14). While living with HMB, easy bruising, frequent epistaxis, post-partum hemorrhage and other bleeding symptoms, many women report that when they seek help for these symptoms they are brushed off and told that their symptoms are "normal".

Some studies report that the average woman with a bleeding disorder first experiences symptoms of prolonged bleeding at age 6. However, the diagnosis may be delayed until age 23 (7). This can lead to psychological manifestations such as anger, anxiety, fear and isolation. If these symptoms are internalized they may lead to depression.

Bleeding disorders can greatly affect health and quality of life. Excessive and prolonged menstrual bleeding may lead to missed school and workdays, isolation, and chronic anemia with lethargy, headaches and other symptoms. (15). Absenteeism due to bleeding episodes may lead to poor school performance, as well as difficulty maintaining employment. Researchers have shown that teens and adult women with HMB report lower quality of life related to the number of days of menstrual bleeding, the severity of bleeding and its impact on their lives (4).

Many women who have a bleeding disorder experience guilt related to their reproductive choices. They may feel as though they should not have children because of the possibility of passing on a bleeding disorder. Their marriage prospects may be affected if the potential partner and their family has lack of understanding about the disorder and its potential impact. Even when a woman who has the hemophilia gene knows that she can have a son with the disorder, many have described feelings or sadness, shock and grief when a son is diagnosed (11).

A challenge for women with bleeding disorders is their tendency to prioritize the care and interests of their children and family, sacrificing their own needs in the process. Joining a parent support group can help provide a new perspective as they see how others cope with the challenges of the diagnosis. Learning that self-care is not indulgent can help with developing the resilience needed to move forward and live their best life (16).

Efforts to alleviate the psychological impact of a bleeding disorders diagnosis involves supporting affected women as they work through adapting to the diagnosis. Assisting them to connect with the social resources of family, friends and community will help with adaptation and allow them to learn to live their lives as fully as possible (17).

Additionally, those who provide care for women with bleeding disorders can provide education to increase awareness of the incidence, severity and impact of bleeding disorders in women to the medical community and the larger world. Efforts to increase understanding of this issue should be directed first towards obstetricians and gynecologists, since they are often the first point of contact for the complaint of prolonged bleeding. Education should also be extended to

the hemophilia community so that mothers, sisters, daughters, cousins and aunts can be offered the opportunity carrier testing and counseling, as well as treatment for their bleeding (2). Hemophilia treatment centers should work to develop and enhance services to meet the physical and psychosocial needs of women with bleeding disorders and to make these service widely available to affected women.

Specialized Care for Women and Girls with Bleeding Disorders

According to the Centers for Disease Control and Prevention (CDC), specialty medical care for all persons with bleeding disorders should be coordinated through a Hemophilia Treatment Center (18). Across the United States more clinics for women and girls who have bleeding are opening and coordinating care with OB/GYN specialists to provide this care. If these specialized clinics are not available, then care should be coordinated with outside gynecologists who specialize in bleeding disorders.

The Foundation for Women & Girls with bleeding disorders (FWGBD) has a great online resource to find specialized clinics throughout the US (19). There is also a wealth of information and resources on women and girls who bleed available on their website to assist providers in managing their care (19, 20).

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