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.

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. Many healthcare providers are not aware of the prevalence of bleeding disorders among females and may believe that prolonged bleeding occurs only in men. However, women can be affected by several different bleeding disorders such as von Willebrand disease (VWD); platelet defects; Hemophilia A, B or C; and other more rare clotting deficiencies, as well as disorders involving the fibrinolytic system.

Regardless of the bleeding disorder diagnosis, females experience a monthly reminder of their tendency to bleed heavily at least 12 times each year. While the manifestations of bleeding in women are not unique to women with bleeding disorders, they may be much more severe. Menorrhagia may lead to increased pain during menstruation, chronic anemia, hospitalizations, the need for blood transfusions, limitations in daily activities, time lost from work and school, 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 young women with bleeding disorders appears to be much greater than that of the general population. (1)

The prevalence of bleeding disorders in females is unknown. However, von Willebrand Disease (VWD), the most common bleeding disorder in humans, may affect between 1% and 2% of the general population. Among those women seeking medical care for menorrhagia, the incidence of VWD or another bleeding disorder may be as high as 20-25%. (2)

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

TYPES OF BLEEDING DISORDERS IN WOMEN

VON WILLEBRAND DISEASE

VWD is the most common inherited bleeding disorder, and it affects men and women equally. VWD follows an autosomal dominant inheritance pattern. Bleeding in VWD is predominantly mucocutaneous, and symptoms of nose bleeding, mouth bleeding and easy

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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 menorrhagia 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 that most women experience. 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 is often reported.

Testing for von Willebrand disease requires close evaluation by a qualified hematology team. There are 3 areas that must be evaluated: the family history of bleeding, personal history of bleeding, and laboratory testing. Making the diagnosis of VWD can be very challenging because of the subjective nature of bleeding symptoms and because of fluctuations in factor levels that may occur on a daily basis. Von Willebrand factor levels fluctuate in all people and can be influenced by several factors including stress, illness, medications and hormones.

Community physicians may know little about testing for von Willebrand disease. The types of blood tests available in the community are not always helpful in making a diagnosis of VWD. Blood specimens collected for coagulation testing must be handled with great care or the specimen degrades, making diagnosis difficult. The specialty testing that is necessary to make a diagnosis of VWD is often performed only at large medical center laboratories. This means that specimens must be shipped to be tested, which provides another opportunity for mishandling of the specimens.

While studies suggest that as many as 15-20% of women seeking care for menorrhagia may have VWD, a 2002 CDC study found that only 4% of gynecologists responding to the survey would consider VWD as a cause of the heavy bleeding. (3) Recent recommendations published in the *American Journal of Obstetrics and Gynecology* encourage providers to suspect VWD when evaluating women for menorrhagia. (4)

SYMPTOMATIC CARRIERS OF HEMOPHILIA

Women who are genetic carriers of hemophilia A or B have one gene affected by hemophilia and one that is unaffected. Factor VIII or IX levels that are approximately half of normal are not unusual among hemophilia carriers. (5) This means that there are a wide variety of factor levels found in females as well as a wide variety of bleeding symptoms.

Women are found to be hemophilia carriers after giving birth to a son with hemophilia and having genetic testing. A woman whose father has hemophilia is considered an "obligate carrier," since the only X chromosome that can be given by the father is affected with the disease. If a woman has a son with hemophilia and any other maternal relative affected by the condition, she is presumed to be a carrier. Women may be born into a family with a long history of hemophilia or may be surprised to discover that they

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are affected by a new 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 have 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. (6) Female carriers who have lower than normal factor levels may be considered to be persons with mild hemophilia.

WOMEN WITH HEMOPHILIA

Although rare, cases of severe Hemophilia A and B are found in women. These 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 experienced extreme lyonization of the hemophilia gene, causing the woman's normal gene for the production of Factor VIII or Factor IX to be "turned off". Women who have moderate to severe hemophilia will have bleeding similar to that of males with the same degree of severity of hemophilia, with the added feature of gynecologic and obstetric problems that make clinical management much more challenging.

RARE BLEEDING DISORDERS IN WOMEN

Factor XI deficiency is a very rare bleeding disorder. Also called Hemophilia C, it affects approximately 1 in 100,000 people in the United States. Those with Ashkenazi Jewish heritage are found to be more frequently affected, leading to higher incidence of the condition in regions with large populations of individuals with eastern European or Israeli heritage. Factor XI deficiency is increasingly being found in persons from all ethnic groups, as well as in those with no family history of bleeding. (7) Factor XI deficiency follows an autosomal dominant inheritance pattern, meaning that males and females are equally affected.

Very little is known about Factor XI deficiency. For reasons that are not well understood, bleeding symptoms do not seem to be directly related to the level of Factor XI found in the blood. Therefore, it can be difficult to predict bleeding symptoms. Prolonged bleeding may occur with surgeries, dental extractions and injury, similar to the bleeding that occurs with von Willebrand disease.

Other rare factor deficiencies may be found in women. Factor V, Factor VII, Factor X and Factor XIII deficiencies may all produce excessive bleeding. Afibrinogenemia, also called Factor I deficiency may produce severe bleeding symptoms. Dysfibrinogenemia is a disorder in which fibrinogen is found in lower quantity as well abnormal quality, leading to prolonged bleeding.

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Platelet dysfunction syndromes may be found in women. Moderate to severe bleeding can be seen in conditions such as Bernard-Soulier syndrome and Glanzmann Thrombasthenia. The milder platelet storage pool or platelet aggregation dysfunctions can also lead to bleeding with surgeries, dental extraction and injuries, with a bleeding pattern is similar to that of von Willebrand disease. (8)

Disorders of hyperfibrinolysis, or excessive early breakdown of blood clots, can lead to bleeding symptoms in men and women. One such disorder is that of plasminogen activator inhibitor type I (PAI-1) 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. (9)

TREATMENT OF GYNECOLOGIC AND OBSTETRIC BLEEDING

The non-gynecologic symptoms of bleeding in women, such as bruising, epistaxis, joint and soft-tissue bleeding, and 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 menorrhagia, dysmenorrhea, painful ovulation, postpartum bleeding, and hemorrhage following abortion (spontaneous or therapeutic).

MENORRHAGIA

Menorrhagia is defined as menstrual blood loss exceeding 80 ml per cycle, but 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. Various pictorial charts have been developed to assist in screening for menorrhagia, with reported predictive value of 75-85%. (10) The charts require that the patient record the number of days of menstrual flow, as well as the number of feminine hygiene products and level of saturation of the products used each day. Many women with bleeding disorders experience menorrhagia beginning with the first menstrual cycle.

In 2007, the National Institute for Health and Clinical Excellence (NICE) defined menorrhagia as “excessive menstrual blood loss which interferes with the woman’s physical, emotional, social and material quality of life, which can occur alone or in combination with other symptoms.” (11) The group further said that “any interventions should aim to improve quality of life measures.”

A variety of treatments are available, including hormone therapies, desmopressin acetate (DDAVP), antifibrinolytic agents, and replacement clotting factors. Often combination therapy is required to adequately control menorrhagia. Surgical intervention should be a treatment of last resort.

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Estrogen raises the level of clotting factors II, VII, VIII, X and von Willebrand factor (VWF). Estrogen can be conveniently administered in the form of oral contraceptive pills and patches. Hormone therapy can be helpful in treating menorrhagia 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 Mirena IUD (12) and progestin shots (Depo-Provera injection) can also be effective in treating menorrhagia with hormone therapy.

Desmopressin acetate (DDAVP) may help raise circulating levels of Factor VIII and VWF in many women with mild to moderate hemophilia A and type I von Willebrand disease. Some women with type II VWD can also use DDAVP. Testing should be performed prior to using DDAVP to insure that the factor levels will increase with its use. Stimate (DDAVP in nasal spray form) can be quite convenient for women to use in treating bleeding episodes. 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.

Antifibrinolytic 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 menorrhagia. 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 who have factor deficiencies for which virally attenuated factor concentrates exist should be prescribed the clotting factor. When no virally attenuated products are available, cryoprecipitate or fresh-frozen plasma may be used. Women who use factor regularly should be given the option of learning 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 menorrhagia. Endometrial ablation may be a safer procedure for the treatment of menorrhagia because it is not as invasive as hysterectomy. However, it is not always effective in long-term control of heavy menstrual bleeding. Since both hysterectomy and endometrial ablation will render the woman sterile, the woman's reproductive plans 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. 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 in the abdominal cavity will bleed, sometimes excessively, each month with menstruation. Free blood in the abdomen can cause severe pain. Treatment of painful menstruation often

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requires the use of non-steroidal anti-inflammatory drugs (NSAIDs), which may actually worsen the condition. Many NSAIDs cause platelet dysfunction, which results in worsening of bleeding symptoms. 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. 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 or early diagnostic options are available for the infant; and medical management of the pregnancy, delivery and postpartum period. Ideally 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. Conditions such as von Willebrand disease and platelet dysfunctions 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. 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 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 be sure that they will have a child who 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. Because of this, women with bleeding disorders will often have improved hemostasis and fewer bleeding symptoms while pregnant. (13) 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.

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

Advice about method of childbirth 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 physicians recommend that cesarean section is the preferred route of delivery if severe hemophilia is suspected. All of those knowledgeable about bleeding disorders strongly insist that instrumental delivery and the use of suction be avoided if the fetus is at risk of having a bleeding disorder. Obviously, if surgical delivery is required, the mother should be treated to prevent bleeding with the surgery.

Coagulation factors will remain elevated for a period of time after delivery, although this might vary from woman to woman. Post-partum hemorrhage is not unusual in women and may have a higher incidence in women with bleeding disorders. Some studies suggest that the incidence of post-partum hemorrhage in women with bleeding disorders may be as high as 22% as compared to 5% in the general population. Of note, late post-partum hemorrhage (day 5-14) is reported as being frequent in women with bleeding disorders, so attention to this issue is advised. (4)

Infertility is defined as difficulty getting 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 unknown 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 VIII and von Willebrand factor levels that occur soon after the loss of a pregnancy. Good hematologic care is advised during and after miscarriage.

PSYCHOSOCIAL ISSUES

Bleeding disorders can greatly affect health and quality of life. Women who experience chronic menorrhagia often have iron-deficiency anemia, leading to lethargy, headaches, and other symptoms, and may even require blood transfusions as treatment. Many report that when they seek help for the symptoms of a bleeding disorder, they are brushed off or told that their symptoms are “normal.” Some medical providers persist in believing that only men have bleeding disorders, and this leads to under-recognition of the diagnosis and severity of bleeding. Women with bleeding disorders are more likely to have surgical treatment, including hysterectomy, and at an earlier age than those without bleeding disorders. (12)

Absenteeism due to bleeding episodes, especially menorrhagia, may lead to poor school performance and difficulty obtaining and maintaining employment. Researchers have shown that teens and adult women with menorrhagia report decreased quality of life

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related to the number of days of menstrual bleeding, the severity of the bleeding, and its impact on their lives. (14)

Some studies report that the average woman with a bleeding disorder first experiences symptoms of prolonged bleeding at age 6, but that diagnosis may be delayed until age 23. (15) This can lead to psychological manifestations such as anger, anxiety, fear, and isolation. If these symptoms are internalized, they may lead to depression and other psychological problems.

Efforts to alleviate the psychological impact of bleeding disorders in women should involve increasing awareness of the incidence, severity, and impact of bleeding disorders on women in the medical community as well as in the larger world. Education should be directed towards obstetricians and gynecologists, since they are often the first point of contact for the complaint of prolonged bleeding. Education should be extended within the hemophilia community, since many carriers of the condition do not know that they should be evaluated and treated for the bleeding they experience. Additionally, 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 services widely available to affected women.

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