

GYNECOLOGICAL COMPLICATIONS IN WOMEN WITH BLEEDING DISORDERS

Revised Edition

Renée Paper

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Treatment of Hemophilia Monographs
Series Editor
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Gynecological Complications in Women with Bleeding Disorders

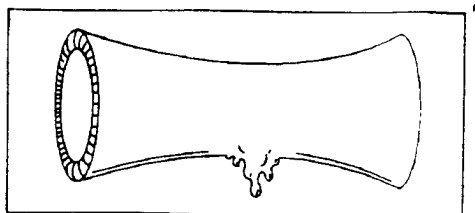
Renée Paper

Introduction

Bleeding problems among women are often unrecognized or misdiagnosed. While they are in fact a common problem, very little information is available regarding gynecological complications for this population. In this article I provide some information that I have researched as well as anecdotal information for women who are seeking answers to persistent problems. Much of the information I present about the diagnosis and treatment of specific bleeding problems has been garnered from interviews conducted over the last eight years with women affected by bleeding disorders from throughout the world.

Simplified Review of Hemostasis

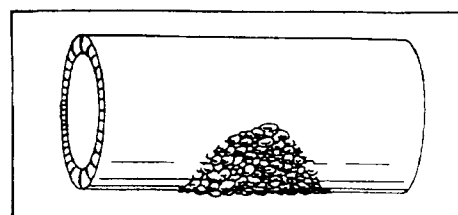
Vasoconstriction. This is the first step in hemostasis (the termination of bleeding) where the blood vessels constrict or narrow in the injured area in an effort to decrease the flow of blood (Fig.1).



Vasoconstriction Fig. 1

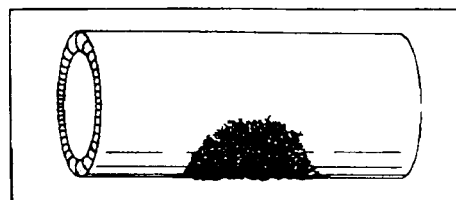
Platelet plug formation. Through a series of chemical reactions, platelets rush to the site of injury, adhere to the vessel wall, and aggregate or stick to each other in an effort to plug the injury in the vessel wall (Fig. 2). Many chemicals and proteins are involved in this process but one of the most important is von Willebrand factor (vWF). VWF is a glue-like protein whose functions include acting as a carrier and protector for factor VIII in the bloodstream and assisting with platelet adhesion and aggregation. (A quantitative deficiency or a qualitative defect of this protein results in von

Willebrand disease.) The platelet plug is only a temporary plug, which requires reinforcement with the fibrin clot.



Platelet Plug Fig. 2

Fibrin clot formation. In this step a mesh-like covering over the platelet plug known as a fibrin clot (blood clot) is formed via the interaction of the 10 plasma-clotting factors numbered by Roman numerals I to XIII (Fig. 3). A deficiency of any one of these proteins can result in a delay or incomplete formation of the clot and subsequent re-bleeding.



Fibrin Clot Formation Fig. 3

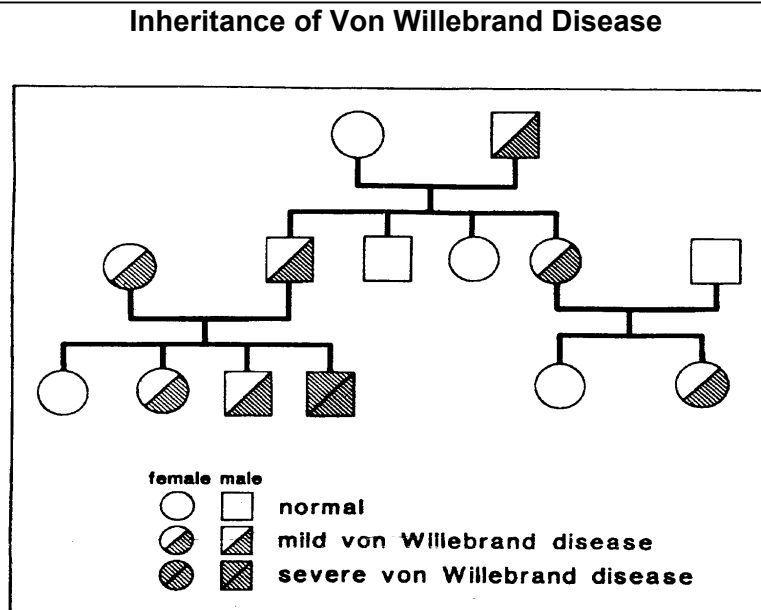
Bleeding Disorders Affecting Women

Bleeding disorders can be inherited or acquired during a person's life. Certain types of medications, treatments, malignancies, and autoimmune disorders can cause acquired bleeding disorders. Focusing on the inherited disorders, what follows is an outline of the most common bleeding disorders in women.

Von Willebrand disease

Von Willebrand disease (vWD) is a very common inherited bleeding disorder with an estimated prevalence of 2% of the population or one in 50 people. vWD is found worldwide among people of all socioeconomic and ethnic groups. It is an autosomal disorder affecting males and females

Fig. 4



The presence of von Willebrand Disease (vWD) is determined by a gene passed down from parent to child. The abnormal gene in vWD is on one of the regular chromosomes, not on one of the sex chromosomes (as in hemophilia) and therefore vWD occurs with equal frequency and severity in males and females. Often a careful family history will assist the clinician in suspecting the condition. Occasionally, the abnormal gene may appear for the first time in a patient when neither parent has the abnormality. This may be due to a new "mutation", and the disorder could then be passed on to subsequent children in the usual manner. Or perhaps, the condition was present but the patient did not become symptomatic until challenged with surgery, injury, menstruation or childbirth. It is very possible to live a normal life with mild VWD and not know the disorder is present until severe bleeding challenges the body. Specific testing of the von Willebrand factor gene (DNA) is now possible for some forms of von Willebrand Disease.

It is sometimes possible to trace vWD through several generations. The figure above demonstrates the usual pattern of dominant inheritance. Although the genetic defect is inherited in an autosomal manner, it does not fit the classical patterns of autosomal dominant or autosomal recessive. Type 1 vWD and some of the variant forms of the disease (Type 2A or 2B) appear to follow autosomal dominant patterns, but severe vWD (undetectable levels of von Willebrand factor) is usually only seen when two genes are defective. It is also possible to inherit two different defective VWF genes, such as inheriting the Type 1 VWD from one parent and the Type 2A VWD gene from the other parent. Such persons would be classified as having a mixed form of VWD Type 1/2A.

Reprinted with permission from *Understanding von Willebrand Disease*, published by the National Hemophilia Foundation (U.S.A.).

equally, however, females with VWD often face additional challenges due to excessive bleeding in conjunction with their menstrual periods and following childbirth. (Fig. 4)

VWD is classified into three main types according to whether the defect in von Willebrand Factor (vWF) is quantitative (amount) or qualitative (quality or function). Type 1 vWD involves a deficiency of vWF. Type 2 vWD, of which there are four subtypes, involves a qualitative defect of the vWF (it does not function properly). Type 3 involves a near or complete absence of vWF. Most types are inherited in an autosomal dominant manner. Type 3 and 2N are inherited in a recessive manner. It is important to know which type of vWD the individual has, because the treatment varies among the specific types. If there is a significant decrease in vWF as seen in Type 3 or

a problem with the vWF binding to factor VIII as seen in Type 2N, then a significant decrease in Factor VIII levels may also be found. Sometimes people with vWD Type 3 or 2N are erroneously diagnosed as Hemophilia A because of a significantly decreased factor VIII. To prevent such as misdiagnosis, it is imperative when evaluating someone for the presence of a coagulation disorder that the level of both factor VIII and vWF be checked.

Symptoms of vWD relate to the body's inability to form a platelet plug. The bleeding is mainly mucocutaneous (mucous membrane and skin). The most common symptoms are easy bruising, frequent or prolonged nosebleeds, heavy or prolonged menstrual bleeding (menorrhagia) and prolonged bleeding following injury, surgery, dental work and childbirth. Gastrointestinal bleeding can also occur. Joint

bleeding in vWD is much rarer than in hemophilia and usually occurs in individuals who also have a low factor VIII level. Contact your local or national hemophilia organization for additional information on the inheritance, diagnosis and treatment of vWD.

The hemophilias

Because the inheritance pattern of both hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are x-linked recessive, females rarely have either of these disorders. However, female carriers of hemophilia A or B may themselves exhibit symptoms of prolonged bleeding because their factor VIII or IX levels may be abnormally low. These carriers are often referred to as "symptomatic carriers." Since most of the medical community is not familiar with this term a more descriptive and accurate term is "mild hemophilia" since the factor VIII or IX levels of these carriers often ranges from 6-35%, putting them into the category of mild hemophilia. Just like males with mild hemophilia these female carriers require treatment when faced with prolonged bleeding whether from their menstrual period or in conjunction with an injury or surgery. Clinically there is no difference between males and females who have abnormally low levels of factor VIII or IX except that females may also suffer from excessive bleeding in conjunction with their menstrual periods and following childbirth.

Miscellaneous disorders

A deficiency of any of the plasma clotting proteins can yield symptoms of varying severity, as can quantitative and qualitative platelet disorders. Most platelet disorders will mimic the symptoms of von Willebrand disease with prolonged mucocutaneous bleeding. Some clotting factor deficiencies cause little if any symptoms (such as factor XII deficiency). Others such as hypofibrinogenemia (a deficiency of factor I) are especially troublesome. With the exception of hemophilia A and hemophilia B (factor VIII and factor IX deficiencies) deficiencies of all of the other plasma clotting proteins are inherited in an autosomal manner, meaning they can affect both males and females. Some are inherited in a recessive manner, others in a dominant manner.

Gynecologic Symptoms Seen in Women with Bleeding Disorders

Menorrhagia/Metrorrhagia

Prolonged and heavy menstrual bleeding is the most common hemorrhagic complication reported by women with bleeding disorders. Some bleed excessively during the menstrual cycle (called menorrhagia); others bleed right through the menstrual cycle (metrorrhagia). The uterus is a very vascular organ and is capable of losing a great deal of blood in a short period of time. With prolonged bleeding iron deficiency anemia may occur. Therapeutic interventions such as dilatation and curettage (D&C) will usually only worsen this problem since scraping the lining of the uterus disrupts any platelet plugs or fibrin clots that may be in place, leaving a raw uterine surface making it difficult for hemostasis to begin again.

Dysmenorrhea & mid-cycle pain

Another common complaint from women with bleeding disorders is pain during menstrual periods and pain at mid-cycle. The cause can only be hypothesized since no scientific data exists. Some women may have pain due to the sheer volume of bleeding and incomplete clots forming in the uterus. Others report pelvic and generalized abdominal pain when they have co-existent endometriosis. Endometriosis is an abnormal condition in which growth of endometrial tissue occurs in the abdomen outside the uterus. When any woman menstruates, endometrial tissue – wherever it is found in the body – will bleed. If a woman has a clotting defect as well as endometriosis, the tissue found outside the uterus may bleed excessively, causing peritoneal irritation (irritation of the lining of the abdominal cavity).

It is also possible for a woman with a bleeding disorder to bleed excessively at the time of ovulation and experience a great deal of pelvic pain. When the ovum bursts out of the ovary the tiny amount of bleeding that occurs in normal women may be greatly magnified in a woman with a bleeding disorder. In one case I met a woman with vWD Type 3 who bled so excessively during ovulation, she was kept on oral contraceptives for life in order to inhibit ovulation. These are the most likely causes of much of the pelvic and abdominal pain reported

by women with bleeding disorders during the menstrual cycle.

Conception/Fertility problems

Many women with bleeding disorders are on birth control pills or other hormonal therapy. Obviously this will affect a woman's ability to conceive. The long-term impact of such prolonged hormonal therapy on conception is unknown. Some women report excessive bleeding with intercourse, which may also cause difficulty in conception. It is also not known whether the vWF deficiency has any effect on the ability of a fertilized embryo to implant in the uterus; this in turn could affect conception and the ability to carry a fetus to term. Anecdotally there seems to be a higher incidence of miscarriage in women with vWD than in the general population. This may simply be because when spontaneous abortion occurs, the excessive bleeding that follows leads women to seek medical care and a diagnosis of spontaneous miscarriage is confirmed, whereas in the general population, many women spontaneously abort early in pregnancy without ever knowing they were pregnant. The bleeding that follows spontaneous abortion may be severe since the higher levels of many of the plasma clotting proteins that occur during pregnancy fall abruptly after loss of the fetus.

Bleeding following childbirth can be a problem for women with bleeding disorders. Pregnancy usually causes a rise in all of the plasma clotting proteins except factor IX, so often there is no problem with bleeding during pregnancy. However, following childbirth these levels may fall rapidly and lead to post partum bleeding. There is a higher incidence of both primary (immediate) and secondary (delayed) post partum hemorrhage in women with vWD. It is not known if breast-feeding affords any protection in preventing post partum hemorrhage in women with inherited bleeding disorders. Because Type 2 vWD involves a problem with the structure or function of VWF, pregnancy will afford little protection to women with Type 2 vWD, because even though their vWF levels rise, the structural defect is not corrected. Likewise, because women with Type 3 vWD make little or no vWF, pregnancy will not cause a rise in the level of vWF. Because of this women with Type 2 and 3 vWD usually

require treatment to prevent post partum hemorrhage.

Diagnosing an Inherited Bleeding Disorder

For physicians who are not hematology specialists, including obstetrics/gynecologists and family practitioners, establishing the diagnosis of a bleeding disorder can be difficult at best. Most primary care physicians are dependent upon the PT and PTT blood tests and to a lesser extent on Ivy Bleeding Time for the diagnosis of a bleeding disorder. The problem with this assumption is that the most common bleeding disorder in women, vWD, cannot be diagnosed with any of these tests.

In vWD the PT (protime) test is always normal and the PTT (partial thromboplastin time) test is only prolonged when the woman also has a decreased factor VIII level, usually below 40%. A prolonged PT test will only be evident when the problem is with factors I, II, V, VII, X. The PTT test will only be prolonged if the patient has a deficiency of factor I, II, V, VIII, IX, X, or XI. Because the PT and PTT do not evaluate the adequacy of primary hemostasis, and vWD is a problem with primary hemostasis, these tests are not useful for screening a patient for vWD. The Ivy Bleeding Time (BT) may be normal or prolonged. The BT is not a very accurate test, the results are not easily reproducible and it is wrought with technical problems. It is a cursory test to evaluate platelet function and can be affected by many factors such as cold and shivering. A bleeding patient with a normal BT still needs to be evaluated for the cause of their bleeding and a bleeding patient with a prolonged BT still needs further evaluation to determine the cause of the bleeding and prolonged BT. Therefore, the BT is really a useless test since it does not specifically diagnose any disorder or exclude any disorder. Testing for vWD must include the Ristocetin Co-factor assay, which evaluates the function of vWF, the vWF Antigen, which measures the level of vWF and a factor VIII level. Many clinicians also perform tests to evaluate vWF's collagen binding ability. Additional tests such as vWF multimer analysis to examine the protein's structure are especially useful in delineating the different subtypes of Type 2 vWD. There is no

one perfect test for diagnosing vWD. A new, rather inexpensive test, to screen for primary hemostatic disorders, called the Platelet Function Analyzer (PFA-100) is useful for widespread screening of patients for the presence of a primary hemostatic defect, but is not specific as to what the disorder is, i.e.: vWD or some other platelet problem. However, since Ristocetin co-factor, vWF antigen and vWF multimer tests are not readily available in most community and hospital-based labs, the PFA-100 is useful as a general primary hemostasis screening tool, certainly better than the BT, PT and PTT.

Laboratory evaluation for vWD is frequently normal or inconclusive and may require repeat testing for confirmation. People with vWD may have cyclical variations in their levels making diagnosis difficult, especially in those mildly affected. The timing of testing is important. It is best to test women during their menstrual cycle when their hormone levels and subsequently their factor VIII and vWF levels are lowest. When performing coagulation testing it is important to eliminate any environmental or medication influences that can interfere with the accuracy of the testing. Hormone therapy such as oral contraceptives, because of their stimulatory effect on vWF and factor VIII levels, needs to be stopped prior to testing. The use of certain prescription and over the counter medicines that interfere with platelet function must also be stopped. These include aspirin and most non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, Motrin, Advil and Aleve. Because of the many things that can interfere with the accuracy of testing and the normal variations that can occur in factor levels, it is imperative to repeat testing in women with normal lab results but a history suggestive of a bleeding disorder. It is also beneficial to refer women to hematologists who have expertise in the evaluation and management of coagulation disorders. These hematologists are usually affiliated with Hemophilia Treatment Centers (HTCs), which are found throughout the U.S. and worldwide. The specialized tests required to establish the diagnosis of a coagulation disorder usually require the utilization of specialized equipment, reagents and technicians. Laboratory errors during the evaluation of coagulation disorders are common among non-specialized labs.

Utilizing laboratories not specialized in the evaluation of people with hemorrhagic disorders is a tremendous waste of time and money. Hemophilia Treatment Centres are best equipped to perform these evaluations.

Treating Gynecologic Complications in Women with Bleeding Disorders

The following therapies have been successfully used to manage prolonged bleeding in women with bleeding disorders. This list may not be complete so please consult a physician to determine the appropriate treatment for your situation.

Hormone therapy

Oral contraceptives (OCs) are very effective in raising the level of all clotting factors except factor IX. For this reason they are especially useful in managing heavy menstrual bleeding as well as other bleeding in women. Women frequently report that during the week when they are menstruating and taking the placebo pills, they also have an increase in bruising and nosebleeds, which quickly decreases once the contraceptives are started again. For symptomatic carriers of hemophilia A (factor VIII), OCs may be the only therapy required. For women with qualitative vWF defects, the effectiveness of OCs diminishes, since the hormones raise the level of vWF but do not correct the inherent structural defect. For these women, OCs will probably still be of some benefit in helping to regulate their menstrual periods and to diminish the amount of bleeding, but other therapies may also be necessary.

For bleeding that is not responsive to OCs, the use of pure progestational agents such as *Norlutate* and *Provera* can be very helpful because they cause a thickening of the uterine lining (a secretory myometrium) and stop the bleeding. The question here is, how long can you inhibit menstruation? Some practitioners prefer the use of injectable progestational agents such as *Depo-Provera*, though the results reported by women are mixed. The injectable agents are not preferred for a number of reasons: (1) they require an intramuscular injection which is not advised in people with bleeding disorders; (2) if there are side-effects, once the drug is administered, it is in the body

for a few months versus the much shorter half-life for oral agents; (3) the dosage can be controlled better with oral administration. For acute life-threatening bleeding, the use of intravenous conjugated estrogens (*Premarin*) can be effective.

Desmopressin acetate

This medication is available in an injectable form for intravenous or subcutaneous injection (DDAVP injection) and a high potency intranasal form (*Stimate* nasal spray). It is chemically related to the antidiuretic hormone (*vasopressin*). Desmopressin causes a rapid rise in the circulating plasma levels of factor VIII and vWF by stimulating the release of these proteins from the lining of blood vessels. It is very effective in controlling bleeding for women with Type 1 vWD and in women with factor VIII deficiency, such as symptomatic hemophilia A carriers. It is less helpful for Type 2 vWD because it does not correct the structural or functional defect of the vWF. It is of no value in Type 3 vWD where virtually no vWF is produced, and it should not be used in Type 2B because of the excessive platelet binding and subsequent thrombocytopenia it causes. (Thrombocytopenia is a bleeding disorder characterized by a marked decrease in the number of platelets.) Unfortunately, desmopressin is of no value for women who are symptomatic carriers of hemophilia B because it has no effect on factor IX. When prescribing the high potency nasal spray, *Stimate*, physicians need to specify "no substitutions" as there is a less concentrated formula of intranasal desmopressin called DDAVP nasal spray available for treating nocturnal enuresis (nighttime bedwetting) and diabetes insipidus. This less concentrated nasal spray is inadequate for treating bleeding disorders.

Plasma products

For women with bleeding that is not responsive to desmopressin or aggressive hormone therapy, replacement of the deficient or defective clotting protein becomes necessary. Today with the advent of safer, virally inactivated, lyophilized plasma products (factor concentrates); the administration of random-donor blood products such as cryoprecipitate or fresh frozen plasma is unacceptable in areas in which virally attenuated concentrates are available. The U.S. National Hemophilia Foundation Medical and

Scientific Advisory Council, has recommended that random-donor products not be used if other virally attenuated products are available. In the U.S. and elsewhere there are virally safe and hemostatically effective products available for the treatment of bleeding associated with deficiencies or defects of factors II, VII, VIII, IX, X, and vWF. In the U.S. the two most widely used products for vWD are Humate-P (Haemate-P elsewhere in the world) and Alphanate SD. These are both concentrates containing factor VIII and von Willebrand Factor. Monoclonally antibody purified or recombinantly engineered factor VIII concentrates should not be used for vWD because they contain no vWF

Anti-fibrinolytics

Medications such as *Amicar* (aminocaproic acid) and *Cyklokapron* (tranexamic acid) can be of value in managing heavy menstrual bleeding as well as mucous membrane bleeding in the nose and mouth. These medicines do not form a clot they simply keep a clot in place longer once it has formed by blocking the enzymes responsible for fibrinolysis (the natural process of dissolving a clot once it is formed). These medicines should not be used for joint bleeds or bleeding from the kidney.

NSAID Analgesic pain relievers

Most non-steroidal anti-inflammatory drugs have properties that cause platelet dysfunction. They interfere with the adhesion and aggregability of platelets (i.e., the platelets are unable to stick together to help form a plug). Data exists to show that some anti-inflammatory drugs, choline-magnesium-trisalicilate (*Trilisate*), salsalate (*Disalcid*) and the Cox-2 inhibitors (*Vioxx*, *Celebrex* and *Bextra*) do not interfere with platelet function and therefore may be viable options for use by persons with bleeding problems. These medications are frequently helpful in controlling the pain associated with ovulation and menstruation.

Surgical Options

Endometrial ablation

For women who do not respond to other options, destruction of the uterine lining to prevent menstruation may be an option, though it will leave the woman sterile. It appears to be a

safe alternative to hysterectomy considering the difficulties a woman with a bleeding disorder is likely to face during a hysterectomy. There is scientific data in the literature supporting the safety and efficacy of this procedure for women with a variety of bleeding disorders.

Hysterectomy

For some women who are either minimally responsive or totally unresponsive to other therapies, hysterectomy may be the only viable option. Vaginal or abdominal hysterectomies have been safely performed on women with bleeding disorders after adequate and appropriate coverage with factor concentrates. It is imperative that before a woman with menorrhagia is offered a hysterectomy she is first screened for the presence of an inherited bleeding disorder and offered conservative medical management of that disorder. Because of the frequency of hysterectomy as an option for managing menorrhagia and the frequency of vWD in women with menorrhagia (13-20%) the American College of Obstetricians and Gynecologists has made just such a recommendation to their members.

Laparoscopy

For women troubled by pelvic pain due to endometriosis (bleeding from endometrial tissue which grows outside the uterus), the removal of the migratory tissue using a laparoscopic technique may prove helpful. In this procedure, two very small incisions are made into the abdominal wall. An illuminated tube guides the surgeon through one incision while the tissue is removed via the second incision. For women with inherited bleeding disorders some sort of pre-treatment using either desmopressin or clotting factor concentrates will be required prior to any invasive procedure.

Dilatation and Curettage (D&C)

The D&C procedure entails the opening of the cervix and the scraping of the endometrium or lining of the uterus. The use of D&C with the intent of decreasing the amount of bleeding may not be effective for women with bleeding disorders as it removes any existing platelet plugs and fibrin clots from the uterus. Unless the D&C is being performed for diagnostic purposes, it is probably not going to be helpful and may even be harmful.

Oophorectomy

Oophorectomy or removal of the ovaries may be an option for women troubled by ovulatory bleeding who are not responsive to hormonal or other therapy or who are having problems with the side effects of therapy. However, this procedure will not only leave the woman sterile, but will also induce menopause.

It is imperative that women considering any of these options fully understand the risks, benefits and alternatives before consent is given.

Conclusion

I hope this article proves helpful to women and their practitioners as they seek answers to some of the problems faced by women with bleeding disorders. I also hope the article raises many questions, which the medical and scientific community will subsequently attempt to answer. Since this article was first published in 1996 many studies into the management of women with bleeding disorders have been undertaken, but many questions remain unanswered. The time has come to appropriate the necessary resources to adequately answer these questions.

About the Author

Renée Paper has von Willebrand disease, is a registered nurse, and Executive Director of the Hemophilia Foundation of Nevada (U.S.A.).

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Additional Resources

1. "Females Bleed Too." *HANDI Quarterly* (Fall 1993).
2. "Symptomatic Carriers." *HANDI Quarterly* (Fall 1994).
3. Medical and Scientific Advisory Council "Recommendations Regarding Women With Bleeding Disorders." *Medical Advisory* #303 (1997), National Hemophilia Foundation.
4. Medical and Scientific Advisory Council "Treatment of von Willebrand disease." *Medical Advisory* #314 (1998). National Hemophilia Foundation.
5. Bottini, E., et al. "Prevention of Hemoperitoneum during Ovulation by Oral Contraceptives in Women with Type III von Willebrand disease and Afibrinogenemia. Case Reports." *Haematologica* 76 (1991): 431-33.
6. Brenner, PF, Ed., "Management of Bleeding Disorders in Women, The Role of the Obstetrician/Gynecologist." *American Journal of Obstetrics and Gynecology*. (1996): Suppl. 175(3) Part 2. 761-792.
7. Bunschoten, E. P., et al. "Bleeding Symptoms in Carriers of Hemophilia A and B." *Thrombosis and Hemostasis* (Germany) 59, no. 3 (1988): 349-352.
8. Caldwell, David, et. al. "Hereditary Coagulopathies in Pregnancy." *Clinical Obstetrics and Gynecology* 28, no. 1 (March 1985).
9. Conti, M., et al. "Pregnancy in Women with Different Types of von Willebrand disease." *Obstetrics and Gynecology* 68 (1986): 282.
10. Cohen, S., et al. "Epidural Analgesia for Labor and Delivery in a Patient with von Willebrand disease." *Regional Anesthesia* 14 (1989): 95-97.
11. Ewenstein, B. "von Willebrand's Disease." *Annual Reviews in Medicine* 48 (1997): 525-42
12. Gomez, A., Lucia, J.F., Perella, M, & Aguilar, C. (1998) Hemoperitoneum caused by haemorrhagic corpus luteum in a patient with type 3 von Willebrand's disease. *Hemophilia* 4, 60-62.
13. Kadir, R. A., Economides, D. L. Sabin, C. A., Owens, D. & Lee C. A., Frequency of inherited bleeding disorders in women with menorrhagia. (1998) *Lancet*, 351, 485-489.
14. Kadir, R.A., & Economides, D. L. (1997). Obstetric management of carriers of hemophilia. *Hemophilia* 3, 81-86.
15. Kadir, R.A., Economides D. L. Sabin C.A., Owens, D. & Lee C. A. (1998) Variation in coagulation factors during menstruation. *Hemophilia* 4, 290. (Abstract)
16. Kadir, R.A., Lee C. A. , Sabin C.A., Pollard, D. & Economides, D.L. (1998) Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. *Hemophilia* 4, 290. (Abstract)
17. Kasper C. K., (1996) Hereditary Plasma Clotting Disorders and their Management. *World Federation of Hemophilia Monograph Series*, 4.
18. Kouides, P "Females with von Willebrand disease: 72 years as the silent majority." *Haemophilia* 4 (1998): 665-676
19. Lee, C.A. "Women and von Willebrand disease." *Haemophilia* 5 (1999): Suppl. 2. 38-45
20. Mannucci, P. M., (1998). Treatment of von Willebrand disease. *Hemophilia* 4, 661-664.
21. Murray E. and Lilicrap, D. "von Willebrand disease: Pathogenesis, Classification, and Management." *Transfusion Medicine Reviews* Vol. X, no 2 (1996): 93-110
22. Ong, Y. L., Hull, D.R., Mayne, E. (1998). Menorrhagia in von Willebrand disease successfully treated with single daily dose tranexamic acid. *Hemophilia* 4, 63-65.
23. Paper, R., Baker J and Larson K. "Women Can Have Bleeding Disorders." Slide presentation. National Hemophilia Foundation. 1999.
24. Paper, R. & Baker, J. (1998). 25 million women worldwide have von Willebrand disease: How do we reach them? *Hemophilia* 4, 307. (Abstract)
25. Paper, R, and Kelley, L. " A Guide to Living With von Willebrand disease" Aventis Behring. 2002.
26. Robertson, L. E., et al. "Hereditary Factor VII Deficiency in Pregnancy: Peripartum Treatment with Factor VII Concentrate." *American Journal of Hematology* 40 (1992): 38-41.
27. Scott, J. P., and R. Montgomery. "Therapy of von Willebrand disease." *Seminars in Thrombosis and Hemostasis* 19, no. 1 (1993).
28. Von Willebrand Working Party of the United Kingdom Haemophilia Centre Directors' Organization (1997) Guidelines for the Management of von Willebrand disease. *Hemophilia* 3, supplement 2.
29. "Von Willebrand's Disease in Gynecologic Practice" *American College of Obstetricians and Gynecologists Committee Opinion* #263, December 2001.
30. Vosburgh, E. "Rational Intervention in von Willebrand disease." *Hospital Practice* (March 1993).