

Bleeding Disorders in Women:



CDC PROGRAM

An ongoing area of research at the Centers for Disease Control and Prevention (CDC) is the extent and impact of inherited bleeding disorders in women.¹ Hemophilia, the most widely known bleeding disorder, is overwhelmingly a disease of males. The bleeding disorders that occur in women tend to be much less severe and specific than hemophilia, making it difficult for physicians and patients to recognize symptoms and diagnose the condition. This area of women's health, therefore, has been largely misunderstood and neglected. In keeping with the mission of NHF to prevent complications and improve the health of people with bleeding disorders, CDC has committed funds and efforts to study bleeding disorders in women.

Defining the Problem

The CDC program for women with bleeding disorders has included a series of collaborative research projects with the goals of establishing the prevalence of bleeding disorders; assessing physician awareness; improving diagnostic testing techniques; and evaluating treatment and management options.

To better understand the population of women with bleeding disorders, CDC began by surveying 75 women with the most common bleeding disorder, von Willebrand disease (VWD), who were receiving care in hemophilia treatment centers (HTCs) across the United States. This internal survey addressed the origin of referral to the HTC, symptoms experienced before diagnosis, diagnostic processes, services provided and perceptions of the HTC care. Four findings were of particular interest: 86% of the women reported a long history of excessively heavy menstrual bleeding (menorrhagia), which was by far the most common symptom; it took an average of ►

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► 16 years from the onset of symptoms until the woman learned she had VWD; more than half of the women had to be tested many times before receiving a diagnosis; and a large proportion of these women underwent surgical procedures, including hysterectomy, to alleviate the discomfort and effects of menorrhagia. This information concurred with long-standing anecdotal reports from hematologists and patients and paved the way for CDC to set a structured research agenda. To bring the plight of women with bleeding disorders to the attention of the medical community, rigorous scientifically collected data were needed for publication in peer-reviewed medical journals.

Since the most common bleeding disorder is VWD, and since the majority of women with VWD experience menorrhagia, the first research question was to determine whether physicians being consulted by women with menorrhagia, typically gynecologists, were aware of bleeding disorders as a possible cause. In collaboration with the Rollins School of Public Health of Emory University, CDC surveyed members of the Georgia Chapter of the American College of Obstetricians and Gynecologists (ACOG) to understand their methods of diagnosis and treatment of menorrhagia and to determine their perceptions of and experiences with bleeding disorders, particularly VWD. The survey revealed that menorrhagia is a very common complaint, and is reported by approximately 10% of gynecological patients in any given year. When this percentage is extrapolated to the US population, about three million women annually have menorrhagia and according to gynecological literature a cause cannot be found for about 50% of women seeking treatment. In the survey, physicians were given a list of conditions, which included VWD, and were asked to rank each condition as a likely, uncertain or unlikely

cause of menorrhagia. Only 3% of the responding physicians would consider VWD as a likely cause of menorrhagia in a woman aged 15 to 44. When asked the question "Given 1,000 women with menorrhagia, in your opinion, how many would be due to an inherited bleeding disorder," the answer, on average, was less than 1%. Although in practice an average of 20 years, 42% of the responding physicians reported never having seen a woman with menorrhagia who had a bleeding disorder.

With a large number of women seeking medical attention for menorrhagia, gynecologists face the dilemma of deciding which women should be tested for a bleeding disorder.

Furthermore, the survey showed that gynecologists virtually never refer a woman with unexplained menorrhagia to another specialist.²

Reports from Sweden and England indicated a higher prevalence of VWD and other bleeding disorders in women with menorrhagia (17% to 37%)^{3,4} than perceived by the physicians in this survey. As a next step in the research agenda, CDC again collaborated with Emory University to perform an epidemiological study to determine the

prevalence of bleeding disorders in a population of American women with menorrhagia in order to corroborate or refute the European findings. The study was conducted with women enrolled in a health maintenance organization during a specified time period. Participants were either of two groups: women with a diagnosis of menorrhagia according to the medical record or were among a random sample of women without the diagnosis who had seen a gynecologist for other reasons. About half of the women in the study were African American. Laboratory testing performed at CDC showed that 8.2% of the women with menorrhagia had VWD or another clotting factor deficiency compared to 0.8% of the women without menorrhagia. To mimic the European studies, the diagnosis of VWD was examined separately for Caucasian and African American women. Significantly, VWD was found in 15.9% of white women with menorrhagia and in only 1.4% of African American women with menorrhagia. Two conclusions could be drawn from the findings of this study: First, the data supported the European studies indicating that the prevalence of VWD and other bleeding disorders in Caucasian women (about 15%) was greater than the less than 1% perceived by gynecologists, and second, the prevalence of VWD may vary by race.⁵

With sufficient epidemiological evidence of a high prevalence of bleeding disorders among women with menorrhagia, coupled with the knowledge that gynecologists were rarely considering bleeding disorders in their list of possible causes, CDC deemed the under-diagnosis of bleeding disorders among women a problem of public health importance. As such the CDC research was directed toward interventions to correct the problem. With a large number of women seeking medical attention for menorrhagia, gynecologists face the dilemma of deciding



which women should be tested for a bleeding disorder. Though, for the patient, coagulation testing entails only drawing a blood sample, the laboratory analysis is nevertheless expensive and must be performed by a laboratory experienced in coagulation. CDC is collaborating with Emory University and the Robert Wood Johnson Medical School to develop a questionnaire designed to help gynecologists determine which patients with menorrhagia are likely to have a bleeding disorder and should be referred to a coagulation laboratory for testing. The questionnaire is being tested and publication is projected for late 2003.

Along with the issue of *who should be screened* for bleeding disorders is a controversial list of *how to screen*. The CDC prevalence study revealed racial differences in VWD. With this discovery, CDC laboratory scientists examined coagulation factors in Caucasians and African Americans without bleeding disorders or other health problems. This research found baseline racial differences in several hemostatic parameters, specifically higher von Willebrand factor and factor VIII in African Americans compared to Caucasians.⁶ Furthermore, preliminary data indicate that platelet disorders are more prevalent in African American women than in Caucasian women. CDC is exploring the diagnostic and clinical implications of these racial differences.

Another question in testing for VWD is whether to consider the menstrual cycle in determining when to test. Von Willebrand factor levels are affected by estrogen. Underdiagnosis of VWD could result if raised estrogen levels, which occur at certain times during the menstrual cycle, give a falsely high reading of von Willebrand factor, thus causing a false negative test for VWD. Until recently, the consensus among hematologists has been to ignore the menstrual cycle when testing for VWD.


However, recent data from CDC indicate that the lowest von Willebrand factor levels are on days one to four of the cycle (during menses) suggesting that this is the best time to test.⁷

Laboratory research into new and better diagnostic procedures and techniques for women with bleeding disorders is ongoing at CDC and elsewhere. Until these new tests are developed, CDC encourages individuals who suspect a bleeding disorder to seek testing from laboratories experienced in coagulation in order to prevent the need for multiple tests to achieve an accurate diagnosis.

Looking to the Future

The CDC research team on women with bleeding disorders was gratified to learn of the December 2001 ACOG committee opinion (see page 42) which recommends screening for VWD in adolescents with severe menorrhagia, adults with unexplained significant menorrhagia and before hysterectomy indicated for excessive menstrual bleeding.⁸ This opinion was undoubtedly the result of consistent, published research by Europeans and by CDC and its collaborating institutions. Now that gynecologists have officially recognized bleeding disorders in women, it can be assumed that diagnosis of these conditions will increase; thus the issues of optimal treatment and management options for women with bleeding disorders arises. In response, CDC has funded and is actively participating in a multi-center study on this topic with Emory University Medical School, Mayo Clinic, Robert Wood Johnson Medical School and University of Rochester Medical School. This study will provide information on diagnostic issues, quality-of-life measures, medical treatments (oral contraceptives, Stimate, Tranexamic Acid) and the role of HTCs in managing women with bleeding disorders. The project is underway and

will be completed in 2004.

The expected impact of the CDC program for women with bleeding disorders is to improve recognition and diagnosis of bleeding disorders, reduce unnecessary surgical procedures for the control of menorrhagia and to improve the quality of life for women with bleeding disorders through proper treatment and management. Ultimately, CDC will urge the development of a national standard for diagnosis, treatment and management for women with bleeding disorders. 

REFERENCES

1. Dilley A, Crudder S. von Willebrand disease in women: The need for recognition and understanding. Observations from the CDC. *Journal of Women's Health and Gender-Based Medicine* 1999;8(4):443-45.
2. Dilley A, Drews C, Lally C, et al. A survey of gynecologists concerning menorrhagia: perceptions of bleeding disorders as a possible cause. *Journal of Women's Health and Gender-Based Medicine* 2002;11(1):39-44.
3. Kadir RA, Economides DL, Sabinb C, et al. Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet* 1998;351:485-89.
4. Edlund M, Blomback M, von Schoultz B, et al. On the value of menorrhagia as a predictor for coagulation disorders. *American Journal of Hematology* 1996;53:234-38.
5. Dilley A, Drews C, Miller C, et al. von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. *Obstetrics and Gynecology* 2001;97:630-36.
6. Miller C, Dilley A, Richardson L, et al. Population differences in von Willebrand factor levels affect the diagnosis of von Willebrand disease in African-American women. *American Journal of Hematology* 2001;67:125-29.
7. Miller C, Dilley A, Drews C, Richardson L, et al. Changes in von Willebrand factor and factor VIII levels during the menstrual cycle. Letter to the Editor. *Thrombosis and Haemostasis* 2002;87:1082-83.
8. ACOG Committee Opinion No. 263. Von Willebrand's Disease in Gynecological Practice. *Obstetrics and Gynecology* 2001;98(6):1185-86.