

von Willebrand Disease: Issues for Women and Men

Chair: Ann-Marie Nazzaro, National Hemophilia Foundation, United States

VWD in Women: Presentation and Identification

Rezan Kadir, Department of Obstetrics and Gynaecology, Royal Free Hospital, London, UK.

von Willebrand disease (VWD) is the most common bleeding disorder, characterized by a deficiency in either the quantity or the quality of von Willebrand factor (VWF). The majority of cases are mild type 1 disease. All types of the disease are autosomal, Dr. Rezan Kadir said, so the expected prevalence should be the same in men and women.

However, the disease's symptoms are often more severe in women because of the frequent and recurring hemostatic challenges that they face, particularly ovulation, menstruation, and childbirth. Furthermore certain gynecological problems such as fibroids, polyps, endometriosis, and ovarian cysts often present with bleeding symptoms or symptoms associated with bleeding. If VWD is not diagnosed, these more or less routine events pose the threat of serious bleeds even in people with a mild form of the disease. The U.K.'s national patient registry indicates that 62% of patients with VWD are women, Dr. Kadir noted.

Menorrhagia (excessive bleeding during menstruation) is the commonest symptom in women. A study in which Dr. Kadir's centre participated revealed that 74% of women with VWD suffered from menorrhagia, compared with 29% in the control group. Most often, menarche (the onset of menstruation) is the event that leads to the first significant bleeding episode and consequent diagnosis of the disease.

During pregnancy, Dr. Kadir said, factor levels increase, so bleeds are relatively rare. Immediately after birth, however, levels go down, which often results in abnormal genital tract bleeding. During menopause, bleeds can be associated with hyperplasia (an abnormal increase in the number of cells) and the thickening of the endometrium. In effect, VWD impacts the lives of women at all ages, both physically and in terms of mental health and quality of life (QoL).

Despite the mounting body of knowledge regarding VWD, delayed diagnosis is still common, probably because of a lack of awareness, even among health professionals. Some studies suggest that as few as 2%-4% of gynecologists consider testing for VWD in women who complain of heavy menstrual bleeding. Dr. Kadir emphasized the need to improve awareness of the disease among medical practitioners and the public, and to disseminate accurate information internationally. The use of a simple screening tool ensures early diagnosis and appropriate treatment, leading to reduced morbidity and improved QoL for women with VWD.

VWD and VWD Prophylaxis Network: A New Treatment Concept

Thomas Abshire, Emory/Children's Comprehensive Hemostasis and Thrombosis Program, Atlanta, GA, United States

Dr. Thomas Abshire presented an overview of an international study involving sites in North America, Europe, and Asia that is to examine the effectiveness of prophylaxis treatment for patients with VWD.

Although several small studies have suggested that prophylaxis can prevent or minimize joint and gastrointestinal bleeds in people with VWD, it is still rarely used, Dr. Abshire said. The VWD Prophylaxis Network (VWD PN) will try to determine the pattern of bleeding in enrolled patients, and the effects of prophylaxis on target joints, gastrointestinal (GI) bleeding, epistaxis (nosebleed), and menorrhagia. It will also assess the impact of treatment on quality of life (QoL) and attempt to determine if any type 3 VWD antibodies or adverse effects develop.

The study will enrol patients with type 3 VWD, type 2B, type 2 with no response to desmopressin (DDAVP), and type 1 with VWF ristocetin cofactor (VWF:RCo) and factor VIII (FVIII) less than 20%. Those enrolled in each category must meet strict bleeding pattern criteria.

At enrolment, participants will be interviewed and categorized according to a broad range of characteristics such as gender, race, ethnicity, bleeding history, and number of hospitalizations. A physical examination will also provide a baseline assessment of target joints and QoL, Dr. Abshire said. Participants will come in every three months for testing and assessments, and will also keep a daily diary tracking infusions and the reason for them.

The study will enrol 50 patients in each bleeding category and will attempt to determine the optimal regimens for each bleeding pattern (joint, GI, mucosal, and menstrual). To date, the study has been initiated at the 14 steering committee members' sites. Dr. Abshire invited new centres to join the study by contacting him at Thomas.abshire@emory.edu.

QoL for Patients with VWD: Nursing Perspective

Lara Oyesiku, Oxford Haemophilia Centre, Churchill Hospital, Oxford, UK

Patient Perspective

Martyn Cooper, United Kingdom

Lara Oyesiku presented the profile of 57-year-old Martyn Cooper, who was diagnosed with type 2A VWD at the age of 11 after a major GI bleed. She described a number of the challenges that his case presented.

Cooper's recurrent GI bleeds require frequent blood transfusions, and he has had many investigatory procedures including angiography, colonoscopies, and bowel resections. He was started on tranexamic acid, which was ineffective. From January 1992 to December 1993, Oyesiku said, Cooper received 235 units of blood.

Having had so many transfusions, Cooper developed antibodies and now requires priton, furosemide, and paracetamol with each transfusion. He also has controlled diabetes. He was prescribed estrogens to reduce bleeding, but the treatment was stopped because of their feminizing effects.

Because Cooper has ischemic heart disease, venous access has often been difficult, so a Port-A-Cath® was inserted, which had to be revised and eventually removed because of complications. Subsequently, an arteriovenous fistula was performed, then revised, but Cooper is still unable

to access it. From 2007 to 2008, he was admitted to hospital more than 40 times, and he still bleeds every 14 days or so.

Martyn Cooper shared some emotional observations. "It's a bit of a miracle that I'm here at all," he said. He described his early years living with the disease, which were relatively uneventful and allowed him to enjoy a fairly normal life and a successful career.

However, his bleeds became more frequent, severe, and difficult to control, and had a pronounced impact on his quality of life. Upon being discharged from a 16-week stay in hospital after surgery, Cooper said, he learned that he had lost his job and his wife had left him "because she didn't want to care for an invalid." He described being depressed and frustrated, and thinking that he had nothing left to live for as his bleeds continued to happen more frequently and various therapeutic approaches failed.

When he had the Port-A-Cath®, he said he felt more in control and more optimistic. As he is unable to access his fistula, his second wife has to infuse him daily. Cooper faces a range of challenges, from physical to financial, but despite all the setbacks, he keeps trying new treatments and therapies: "Do you try each new thing? Of course you do. You keep pushing it uphill whether it works or not. The future doesn't always look too bright and sometimes you're not sure that there is a future, but you just keep pushing on," he said.

Reproductive Concerns and VWD

Andra James, Duke University Medical Center, Durham, NC, United States

Dr. Andra James elaborated on Dr. Rezan Kadir's overview of VWD in women and outlined some key points for therapeutic intervention.

Taking steps in anticipation of the onset of menstruation is extremely important for children or adolescents who are known to have VWD, she said, since many girls bleed extremely heavily during their first period. "Families should have a plan in place in case bleeding occurs, so they know who to call, what to do, where to go, and what the treatment should be."

Management of the menstrual cycle can be especially challenging in adolescents, because they do not necessarily ovulate every cycle, Dr. James said. In the absence of ovulation, the lining of the uterus builds up and can be shed irregularly and heavily.

VWD can be managed with hormonal treatments like oral contraceptives. The Mirena® intrauterine device, which reduces menstrual blood loss and discourages the lining from building up, has shown remarkable improvements in hemoglobin levels. "There is no reason to think this success couldn't be extended to patches and rings, long-term use of oral contraceptives, or continuous contraceptives," she said.

If hormone management fails or if women want to become pregnant, Dr. James said, DDAVP, antifibrinolytics, or VWF are necessary. Planning for pregnancy is also vital, particularly because of the increased risk of postpartum hemorrhage. Women with type 2 or 3 VWD or type 1 with a history of bleeds should have their pregnancies managed in a centre with a knowledgeable anesthesiologist and a specialist in high-risk obstetrics, with a plan for VWF

replacement. Dr. James cited a study by Dr. Kadir that found women with VWD 20 times more susceptible to postpartum hemorrhage than the general population.

Because of the risk of bleeding during invasive procedures such as hysterectomy or dilation and curettage (D&C), alternatives such as endometrial ablation are preferable, Dr. James said. "In women, VWD needs to be controlled from the onset of menstruation throughout the life cycle, and there's a real need to find ways of better managing women's health as they age."

QoL for Patients with VWD: Psychosocial Perspective

Sylvia von Mackensen, Institute and Polyclinic for Medical Psychology, University of Hamburg, Germany

Quality of life (QoL) assessments allow practitioners to describe how a health condition is affecting a patient's well-being and what the effects and impacts of particular treatment strategies are, Dr. Sylvia von Mackensen said. Health-related quality of life (HRQoL), one of the most significant patient-rated outcomes, is finally being acknowledged through its inclusion in various clinical trials.

Assessing HRQoL requires validated instruments, Dr. von Mackensen said. This is still a relatively new field. While several instruments have been developed over the past five years for both adults and children with hemophilia, only recently were attempts made to assess QoL for people with VWD. The first VWD-specific questionnaire (VWD QoL) was designed in Italy and translated into German, with input from both Italian and German patients who participated in focus groups, structured interviews, and written surveys.

Family and social relationships were the most important QoL factors in both the Italian and the German cohorts, Dr. von Mackensen said. Patients consistently said the fear of bleeds was the biggest impairment caused by their VWD, often leading to limitations in leisure activities. They also identified physical problems such as fatigue, epistaxis, and pain, along with some concerns about treatment product safety.

The only significant difference between the German and Italian results was that the German patients mentioned school and pets more frequently, and also cited the impacts on leisure and vacation more often, she said.

The results of these assessments indicate that HRQoL should not be disregarded as a "soft issue," Dr. von Mackensen said. "It is a must-have, especially in patients with chronic disease. With qualitative assessment approaches, comprehensive insight into the disease-related problems that affect patients can be used to help identify their specific health care needs in order to provide appropriate care."