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Research Article

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von Willebrand's Disease is a Condition Characterized by Excessive Bleeding

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ABSTRACT
Von Willebrand disease is a medical condition where individuals experience excessive bleeding. It is typically inherited and results from either a deficiency or an abnormality of von Willebrand factor, which plays a crucial role in the blood clotting mechanism. Generally, those suffering from von Willebrand disease take a longer time to form blood clots, meaning they struggle to stop bleeding. Treatment strategies for this condition mainly aim at preventing or stopping bleeding episodes, often through the use of medication. With proper treatment, individuals can live normal, healthy lives. In women, heavy menstrual bleeding is a common indicator of von Willebrand disease.

Keywords: vWD, vWF, AUB, Types, Health.

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Introduction

Abnormal uterine bleeding (AUB) is often reported, particularly during adolescence and the later stages of reproductive years [1]. As defined by the FIGO classification in 2018, AUB includes changes in the frequency, duration, regularity, and volume of menstrual bleeding. Heavy menstrual bleeding (HMB) refers to a flow volume that negatively impacts a woman's quality of life. However, this is subjective and doesn't necessarily point to a specific medical condition. Long-term, it may lead to iron deficiency and affect overall well-being. Thus, distinguishing between normal and abnormal bleeding patterns is important. Gathering detailed information on the number of sanitary pads used and maintaining a bleeding chart can provide insight into actual blood loss. Women experiencing significant blood loss may also notice passing clots. Previous research shows that normal menstrual bleeding averages around 43.4 mL. Nevertheless, 19% of women report losing over 60 mL, and 11% exceed 80 mL. Notably, a blood loss of 60 mL is strongly linked to the onset of anemia. When assessing a woman with HMB, it's essential to ask about existing medical issues and any medications taken, especially anticoagulants, which should be ruled out.

Von Willebrand disease (vWD) is the most prevalent inherited bleeding disorder among Caucasians, affecting up to 1% of the population [2]. von Willebrand factor (vWF) is a multimeric protein in plasma that plays a role in binding factor VIII and helps with platelet adhesion to the blood vessel lining. Approximately 70% to 80% of individuals with vWD have the classic type (type 1), which is due to a partial deficiency of vWF. In contrast, type 2 involves a qualitative deficiency of vWF that functions abnormally, while type 3 is marked by a nearly total lack

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of vWF. vWD is commonly inherited as an autosomal dominant trait, but it can also show autosomal recessive inheritance. In some cases, the disease can be acquired, often linked with conditions such as hypothyroidism, Wilms tumor, cardiac disorders, renal disease, systemic lupus erythematosus, or the use of valproic acid. Acquired vWD typically arises from the formation of antibodies against vWF or an increased turnover of the factor.

Disorders

AUB in teenagers is often linked to an underdeveloped hypothalamic-pituitary-ovarian axis [3]. While normal adolescent body functions usually account for anovulatory bleeding, it is crucial to rule out other factors such as pregnancy, infections, or trauma. Conditions like von Willebrand disease should also be checked since about half of adolescents experiencing heavy menstrual bleeding could have a bleeding disorder.

For those who have heavy periods starting at menarche, screening for coagulation disorders is essential. Younger adults frequently experience anovulatory bleeding. Signs such as a family history of bleeding issues, heavy periods, frequent nosebleeds, easy bruising, and extended bleeding from small cuts, surgical operations, or dental work should all prompt consideration of von Willebrand disease.

When conducting initial lab tests for women suspected of having a bleeding disorder, a complete blood count with platelets, activated partial thromboplastin time, and prothrombin time are included. If there are positive results indicating a potential inherited bleeding condition, further evaluation for von Willebrand disorder is warranted. Testing for von Willebrand disease is most effective when done with a hematology specialist.

It is projected that around 13% of women experiencing HMB have some form of Willebrand's disease, and nearly 20% might have an underlying coagulation issue [4]. About 50% of women with unexplained HMB have been found to have some degree of platelet dysfunction. Screening for hidden hemostasis disorders is crucial. If a patient tests positive, follow-up lab tests should involve CBC with platelets, prothrombin time, and partial thromboplastin time.

Von Willebrand's disease arises from either insufficient or faulty von Willebrand factor (vWF), leading predominantly to increased mucocutaneous bleeding. The disease typically presents during menarche when anovulatory cycles are frequent and vWF levels are low. If von Willebrand's disease is suspected, further lab tests should check for vWF ristocetin cofactor activity, vWF antigen, and factor VIII. Both inherited and acquired platelet disorders can lead to issues with platelet aggregation, adhesion, secretion, and signaling. Often, inherited bleeding disorders result in prolonged menstrual bleeding and HMB, but they can also aggravate symptoms linked to structural causes of AUB. In cases of coagulopathy-related AUB, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided because they can have lasting effects on platelets; however, COX-2 inhibitors may be appropriate. Tranexamic acid is frequently used in managing bleeding disorders and has proven effective for patients experiencing blood loss.

Von Willebrand Disease

Von Willebrand disease (VWD) is the leading inherited bleeding disorder, affecting both men and women equally, with an overall occurrence rate of about 1% [5]. Many individuals with this condition show no symptoms, although they may have a personal or family history of bleeding issues, including heavy menstrual flows, bleeding during surgery, or postpartum hemorrhage.

The condition arises from a deficiency or malfunction of von Willebrand factor (VWF). This factor is produced by the endothelial cells that line blood vessels and by megakaryocytes, which are the precursors of platelets. VWF has a crucial role in hemostasis in two key ways.

Typically, individuals with VWD exhibit a normal prothrombin time (PT) and a normal platelet count, except in Type 2B, where the platelet count can be low. Their activated partial thromboplastin time (aPTT) may be normal or extended, influenced by the levels of Factor VIII. To diagnose VWD, laboratory tests measure plasma VWF antigen levels, VWF activity (specifically ristocetin cofactor activity), and Factor VIII activity. A diagnosis is confirmed when plasma VWF antigen or activity is low (below 30 IU/dL), and additional tests can determine the specific type of VWD.

In rare instances, VWD can also develop as an acquired condition. This might occur due to antibody-related reductions, often associated with cancers or autoimmune disorders, high sheer stress from conditions like stenotic vascular lesions or hypertrophic obstructive cardiomyopathy, and during treatments such as extracorporeal membrane oxygenation or left ventricular assist devices.

Von Willebrand factor (VWF) is a complex protein that serves two main hemostatic purposes [1].

First, during primary hemostasis at sites of injured blood vessels, it helps platelets stick to the underlying structures and promotes their aggregation to facilitate thrombus formation.

Second, in secondary hemostasis, VWF functions as a carrier for coagulation factor VIII (FVIII), ensuring the stability and activity of FVIII, which is essential for blood clotting.

Von Willebrand Disease (VWD), which stems from a lack of VWF, is the most prevalent inherited bleeding disorder, but diagnosing and treating it continues to pose difficulties. Among Caucasians, the condition affects about 16% of individuals. While 74–92% of women with VWD experience heavy menstrual bleeding (HMB), mild cases of the condition can often go unnoticed since 40% of women who have HMB consider their bleeding to be normal. Additionally, physicians should recognize that 25% of women who have normal blood loss may still perceive their bleeding as excessive. Early identification of a bleeding disorder is crucial for females, particularly to avert complications during childbirth and to manage issues related to injuries or surgical procedures. It is important to increase awareness around this disorder, as only a small fraction of women with HMB currently undergo screening for coagulopathy. Recognizing that bleeding

experiences can be quite subjective has led to efforts to establish standardized diagnostic criteria and methods for gathering data to evaluate bleeding symptom severity and presence. A central question remains regarding which patients with HMB should undergo screening for hemostatic disorders after ruling out gynecologic issues. In the meantime, hematologic societies have introduced a reliable yet intricate scoring system. Gynecologists may prefer utilizing a simpler method, asking key questions to gather a more comprehensive medical history. This is especially pertinent for adolescents, who may not yet have had experiences with childbirth, surgeries, or dental work. As a result, their scores for screening may be lower, even though they could be affected by VWD. Focusing on family medical history is particularly beneficial in this context.

Von Willebrand disease (VWD) is the most frequently identified inherited coagulopathy, with studies indicating a prevalence of 1% to 2% [6]. However, reports based on patients referred due to bleeding symptoms show that clinically significant VWD may occur in 30 to 100 individuals per million. This disease follows an autosomal dominant inheritance pattern and leads to either a decrease in the amount (Type I) or the quality (Type II) of von Willebrand factor (VWF), a crucial multimeric protein for platelet adhesion and the stabilization of plasma factor VIII. Type I VWD accounts for approximately 60% to 80% of cases, while in Type II VWD, although VWF levels are normal, the protein's functionality is impaired, resulting in inadequate hemostasis for 20% to 30% of those affected. Type III VWD, inherited in an autosomal recessive manner, results in almost undetectable VWF levels alongside low factor VIII levels. Despite Type III making up only about 1% of all VWD patients, with an occurrence of 1 in 1 million, its symptoms tend to be more frequent and severe.

Symptoms

Women who have coagulation disorders often experience heavy menstrual bleeding (HMB) starting from their first period [1]. Typically, there is a positive family history associated with HMB. These women may also encounter additional symptoms such as easy bruising from slight injuries, prolonged bleeding from minor cuts, nosebleeds that last over ten minutes or need medical care, frequent gum bleeding, excessive bleeding after dental work, surgical bleeding, gastrointestinal bleeding, and postpartum hemorrhage. They may even have a background of anemia that requires iron treatment. A thorough examination of the bleeding pattern can provide better insight into their condition. Comprehensive screening tools with scoring systems have been created to determine which patients should be referred to a hematologist. For doctors sending a patient for testing related to von Willebrand disease (VWD), it's important to note that von Willebrand factor (VWF) levels can rise when hormonal contraceptives or hormone replacement therapies are used. The hematologist should be consulted about whether it's necessary to pause hormone treatment to ensure an accurate diagnosis.

Clinical Characteristics

VWD is the most frequently inherited bleeding disorder [7]. It occurs due to mutations that either reduce or alter the function of von Willebrand factor (VWF). When there is damage to the endothelial layer, VWF is released from endothelial cells and activated platelets. In the process of primary hemostasis, it helps create links between exposed collagen and platelets, as well as between the platelets themselves, which helps solidify the platelet plug. Furthermore, VWF plays a role in the intrinsic pathway of secondary hemostasis by carrying factor VIII, which is crucial for forming fibrin clots. There are three types of VWD, classified based on increasing severity. Type I involves a quantitative shortage and follows an autosomal dominant inheritance model. In Type II, there is a qualitative deficiency, with both autosomal dominant and recessive inheritance. Type III is characterized by almost no VWF and occurs through an autosomal recessive inheritance pattern.

People with VWD typically display symptoms such as easy bruising, excessive bleeding from small injuries, prolonged mucosal bleeding like nosebleeds or bleeding after dental work, and in severe cases, bleeding in soft tissues and joints. VWD impacts both genders; however, women may experience specific issues such as heavy menstrual bleeding, postpartum hemorrhage, and other medical conditions that involve blood loss.

To identify individuals with a bleeding disorder, a comprehensive medical history is essential. It's important to focus on any history of significant bleeding. Due to the hereditary nature of VWD, gathering a detailed family history regarding any bleeding issues is vital. Checking medication history is also crucial, as antiplatelet drugs can worsen or trigger bleeding. For women, it's especially important to pay close attention to menstrual history since heavy menstrual bleeding is the most common symptom of VWD, reported by 32–100% of affected women. Although VWD occurs in about 1% of the general population, its prevalence rises to 11–16% among women who report heavy menstrual bleeding. This history is particularly relevant for adolescents, since heavy bleeding at the first menstrual cycle, or menarche, can often indicate VWD. The American College of Obstetricians and Gynecologists advises discussing menstrual history during the first reproductive health visit, which typically occurs between ages 13 and 15. This appointment should aim to screen for symptoms of heavy menstrual bleeding that might suggest a bleeding disorder. Clinicians are encouraged to take a quantitative approach when gathering menstrual history, asking questions like the number of pads used and how often they are changed, and may also suggest using a menstrual calendar or pictorial bleeding assessment for better accuracy.

Types

- Type I (80–90% of cases). The levels of vWF are lower than normal, but the factor itself is present [8]. During pregnancy, vWF levels can increase and may even normalize, though this might not hold true for those with severe conditions. After delivery, levels of factor VIII can drop sharply, which could be delayed until the later stages of the postpartum period, resulting in a higher risk of postpartum hemorrhage. Administering desmopressin (DDAVP) intravenously can elevate VIII levels.
- Type II (9–15% of cases). In this type, the von Willebrand factor (vWF) behaves abnormally. As a result, giving DDAVP generally doesn't help improve the coagulation

issues, and the clotting situation remains unchanged during pregnancy. There are several known subtypes, including IIA, IIB, IIM, and IIN. In subtype IIB, the abnormal vWF causes inactivated platelets to clump together, leading to a reduction in platelet count. Here, DDAVP actually worsens the coagulopathy, as the increased abnormal vWF exacerbates the low platelet levels. In subtype IIN (Normandy), a lower factor VIII concentration occurs due to the abnormal vWF having a diminished affinity for factor VIII, which leads to higher consumption of factor VIII. This can be mistaken for haemophilia A.

- Type III (autosomal recessive; 1% of cases). In this condition, vWF is not detectable, and levels of VIIIc are significantly low. The bleeding problem is serious and does not respond to treatment with DDAVP.

Hemophilia

Von Willebrand disease, along with carriers of haemophilia A and B and factor XI deficiency, makes up over 90% of women who have inherited bleeding disorders [9]. Haemophilia A (deficiency of FVIII) and haemophilia B (deficiency of FIX) are linked to the X chromosome, occurring in about 1 in 10,000 and 1 in 100,000 individuals, respectively. Generally, carriers of haemophilia A or B have around 50% of normal clotting factor activity. While factor VIIIC levels rise during pregnancy, factor IXC levels only increase slightly. Von Willebrand disease is the most prevalent inherited bleeding disorder, with a prevalence of about 1%. It arises from either a qualitative or quantitative defect in the von Willebrand factor (VWF). This disease is usually inherited in an autosomal dominant manner. During typical pregnancies, factor VIIIC and VWF antigen activity tend to rise, but this increase cannot always counteract the severe effects of the disease.

Whenever feasible, identifying and advising carriers of haemophilia and women with von Willebrand disease before pregnancy is important. Initial coagulation factor tests should take place as soon as pregnancy is confirmed and should be repeated in the third trimester. For carriers of haemophilia, tests to determine fetal sex should be offered, either through ultrasound or by sampling fetal DNA from the mother's blood, as this affects the choice of interventions during labor.

People with bleeding disorders face a substantial risk of both primary and secondary post-partum hemorrhage, a risk that can be reduced through proper preventative treatment. Delivery planning should involve a multidisciplinary team, including specialists in obstetrics and hematology, and should be informed by clotting factor levels from the third trimester, considering the specific bleeding tendency. Those identified as high-risk should have a care plan drafted, which may include factor concentrate, tranexamic acid, or desmopressin (DDAVP®) during labor and delivery.

For carriers of hemophilia, epidurals may be allowed if their clotting factor levels are deemed sufficient. If there is a chance that the fetus might be affected, invasive fetal monitoring, ventouse, and rotational forceps should be avoided, and cord blood samples should be obtained for coagulation testing.

Management

The treatment selected for von Willebrand disease varies based on its type and the particular situation [10]. For patients identified before birth, a comprehensive evaluation can be conducted to determine the specific type of VWD. For those with types of VWD other than Type 2, a trial of DDAVP might be given at a dose of 0.3 mg/kg intravenously, with von Willebrand factor (VWF) and factor VIII: C levels measured 30 to 60 minutes after administration. If VWF and factor VIII: C levels rise to a normal range, then DDAVP can be used reliably during the later stages of labor, right after delivery, and again 12 hours later. In cases where there is no reaction to DDAVP or when severe deficiencies like Type 2B or Type 3 VWD are present, patients may need replacement therapy with either cryoprecipitate or Humate-P1. The dosing of Humate-P1 is tailored based on the individual's hemorrhage risk or severity. For acute bleeding, an initial bolus of 15 U/kg (factor VIII units) is given, followed by 8 U/kg every 8 hours for the first day, then the same dose every 12 hours for 3 to 4 days. Before delivery or surgery, it is recommended to provide doses of 20 to 26 U/kg. After childbirth or surgery, 15 U/kg every 8 hours should be continued for at least 10 days. Cryoprecipitate usually is given at a rate of 1 to 3 bags per day for every 10 kg of the person's body weight. If neither Humate-P nor cryoprecipitate is accessible, fresh frozen plasma can be administered to elevate factor VIII: C levels to nearly 80% to 100% of normal or to normalize the bleeding time, typically using 10 to 15 ml/kg per day.

The goal in managing VWD is to stop bleeding and manage any complications by boosting levels of VWF and factor VIII [7]. For women, preventative measures focus mainly on reducing heavy menstrual bleeding (HMB). First-line treatment for HMB linked with VWD involves combined hormonal contraception, such as oral contraceptive pills, patches, or vaginal rings. Many women with VWD, about 88%, report that their HMB improves after starting oral contraceptive pills. These pills help raise VWF levels, so lab tests should be done before starting them, as was the case with this patient. The levonorgestrel intrauterine device is also an effective option for managing HMB and works well for women of all ages. Other treatment options include tranexamic acid and ε-aminocaproic acid, both of which are antifibrinolytics that can be used alongside oral contraceptive pills to help control HMB.

Patients with von Willebrand disease are at a high risk of bleeding during invasive procedures. It's crucial to have a preoperative consultation with a hematologist so that lab tests can be performed and a plan for treatment before and after surgery can be established. To manage bleeding effectively, 1-desamino-8-D-arginine vasopressin (DDAVP) can be given to prompt the release of von Willebrand factor from endothelial cells. This medication is meant for short-term use, lasting between 48 to 72 hours. If treatment needs to extend longer, recombinant factor VIII and von Willebrand factor concentrate can be given to address any deficiencies.

Women with von Willebrand disease often experience obstetric complications, making early diagnosis vital. If VWD is identified before conception, these complications can be managed better.

All patients should undergo VWD laboratory testing before any invasive procedures during pregnancy. Testing should also be done in the third trimester to ensure factor VIII and ristocetin cofactor levels are above 50 IU/dL before delivery, extending through 3 to 5 days after. Any patient with type I VWD and factor VIII or ristocetin cofactor levels below 50 IU/dL, along with those with type II or type III VWD, should receive prophylaxis, and delivery should occur in a facility experienced in managing bleeding disorders with specialists available. For immediate replacement during delivery, using von Willebrand factor concentrate is preferred over desmopressin due to the risk of hyponatremia when desmopressin is paired with oxytocin. Because von Willebrand disease follows specific inheritance patterns, all affected women should consult a genetic counselor to understand the disease's genetic effects. Additionally, invasive fetal procedures and operative vaginal deliveries should be avoided as there is a risk of fetal hemorrhage.

Conclusion

Von Willebrand disease is the most common inherited clotting disorder and results from a deficiency or improper function of von Willebrand factor. Symptoms can include frequent nosebleeds, gum bleeding, easy bruising, and heavy menstrual cycles. This congenital condition impacts around 1% of the population. Many cases of von Willebrand disease remain unrecognized in women experiencing menorrhagia or other forms of excessive bleeding. Indeed, menorrhagia is one of the most prevalent symptoms found in women with VWD.

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