ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Current Approaches to Pregnancy and Childbirth in Women With von Willebrand Disease

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H&O How common is von Willebrand disease (VWD)?

JJ VWD is the most common inherited bleeding disorder, with an incidence of approximately 1 per 1000 people. It has an autosomal inheritance pattern, so men and women are equally likely to be affected. Women probably present with VWD more frequently, however, because menstruation and childbirth can lead to excessive bleeding.

H&O What are the various types of VWD?

JJ There are 3 main types of VWD. In type 1—which is the most common by far, accounting for approximately 75% of cases—the level of von Willebrand factor (VWF) is low, but the protein functions normally. In type 2, which accounts for approximately 20% of cases, the VWF level may be normal, but the protein functions abnormally. In type 3, which is the rarest type, almost no VWF is present. Types 1 and 3 are related to the quantity of VWF, whereas type 2 is related to the quality. In all cases, the overall activity of VWF is abnormally low.

H&O How risky is pregnancy for a woman with VWD?

JJ Pregnancy in a woman with VWD is considered high-risk because of the risk for bleeding. The medical management of VWD can reduce this risk, however, and the outcome of pregnancy in most women with VWD is very good. Education and counseling are very important for a woman with VWD who may become pregnant because the pregnancy will require a lot of medical management to reduce the risks to both mother and baby. However, we would never counsel a woman not to have children because of a diagnosis of VWD.

Despite our medical treatments for VWD during pregnancy, we have recently become aware that too many women are still experiencing excessive postpartum bleeding. This finding is prompting us to revisit how we manage these patients.

H&O How common is postpartum hemorrhage in women with VWD?

JJ It is difficult to quantify, but we believe that approximately 20% to 25% of women with VWD have significant postpartum bleeding, even with specific medical care. Some studies have reported a bleeding rate as high as 40%. Regardless of the exact number, we should be paying more attention to this problem.

It is important to remember that hemorrhage may occur immediately postpartum, when the medical staff is present, or weeks later. Both the patient and the healthcare providers must be aware of this possibility. In addition, VWD is not necessarily the cause of postpartum bleeding in a woman who has the disease. The patient must be assessed for other possible causes of postpartum

hemorrhage, such as uterine atony and retained products of conception—the VWD may simply be making the bleeding worse.

H&O Are there specific recommendations for women of childbearing age who do not wish to become pregnant?

JJ This is an especially important question because doctors will often prescribe an oral contraceptive or intrauterine device to a woman with VWD to treat heavy menstrual bleeding, which is very common in women with VWD. If the woman does not begin to use the medication or device for contraception, information about the effectiveness of a specific contraceptive method will sometimes be overlooked. Any woman with VWD must have a conversation with her gynecologist and inform the physician that she is sexually active, so that she can learn about the contraceptive options available to her.

H&O Are there any steps that a woman with VWD should take before planning a pregnancy?

JJ A woman with VWD who wishes to become pregnant should be evaluated by a hematologist. The disease of many patients is diagnosed in childhood and they may no longer be under the care of a hematologist, in which case they need a referral. We want to use modern testing methods to confirm each patient's diagnosis and subtype and establish her adult baseline levels of VWF before pregnancy. During this visit, the hematologist will also describe the typical pregnancy plan for a patient with VWD. If the woman has been pregnant before, the hematologist will be able to learn about any history of bleeding during previous pregnancies. A woman with VWD who is planning a pregnancy also may benefit from referral to a genetic counselor.

H&O Can assisted reproductive technologies, such as in vitro fertilization (IVF), be used in women with VWD?

JJ Yes, they can. IVF is becoming increasingly popular for women experiencing infertility, and that includes women with VWD. IVF does present risks for bleeding related to procedures such as hormone injections, egg retrieval, and manipulation of the cervix or uterus. VWD treatment can reduce the risk for bleeding associated with these procedures. Another risk that health care providers may not be aware of is ovarian hemorrhage, which can be life-threatening. A woman who receives medication to stimulate the ovarian follicles is at increased risk for ovarian hemorrhage. Patients must be counseled that ovarian hemorrhage is one of the risks of IVF, and that immediate medical attention is required if symptoms of abdominal bleeding, such as sudden pelvic pain or pressure, develop.

H&O What are the challenges associated with diagnosing VWD during pregnancy?

JJ Diagnosing VWD for the first time in a patient who is already pregnant is challenging. Pregnancy causes VWF levels to rise in most women, including many of those with VWD, which makes the disease harder to detect (Figure). As a result, the diagnostic evaluation must factor in a history of mucocutaneous bleeding and family history of VWD as well as abnormal results on VWF laboratory tests.

VWF levels trend to increase over the course of a pregnancy, so the more advanced the pregnancy, the harder it can be to make the diagnosis. Testing earlier in a pregnancy increases the odds that you can identify whether a patient has a VWF defect. Even when VWD can be diagnosed for the first time during pregnancy, it is still impossible to determine the patient's pre-pregnancy, baseline level of VWF, which is a useful metric for predicting the severity of later bleeding.

A couple of exceptions apply to these points. First, the VWF level does not increase in all patients with VWD during pregnancy. It is easier to make a new diagnosis of VWD during pregnancy in these women, even if there is no way to establish their baseline level of VWF. Second, some forms of type 2 VWD can be diagnosed via genetic testing, the results of which are unaffected by pregnancy.

H&O How often do women reach adulthood without VWD having been diagnosed?

JJ This happens often, even in women with severe VWD. We see patients who sought medical care for severe hemorrhagic events in the past, and the focus was on the acute crisis—not the potential underlying disease causing the bleeding—even when the family history was positive for VWD. Often, a pregnant woman with VWD will see a hematologist for the first time because an astute obstetrician has detected a history of mucocutaneous bleeding. Data suggest that the diagnosis of an inherited bleeding disorder can be delayed by 20 years or longer from the time of the first bleeding event. When we diagnose a bleeding disorder in a pediatric patient but there is no family history of the disease, it is highly likely that other family members are affected but their disease is undiagnosed.

H&O How does pregnancy affect VWD?

JJ Levels of VWF and factor VIII increase progressively during pregnancy in a woman without VWD, so that by

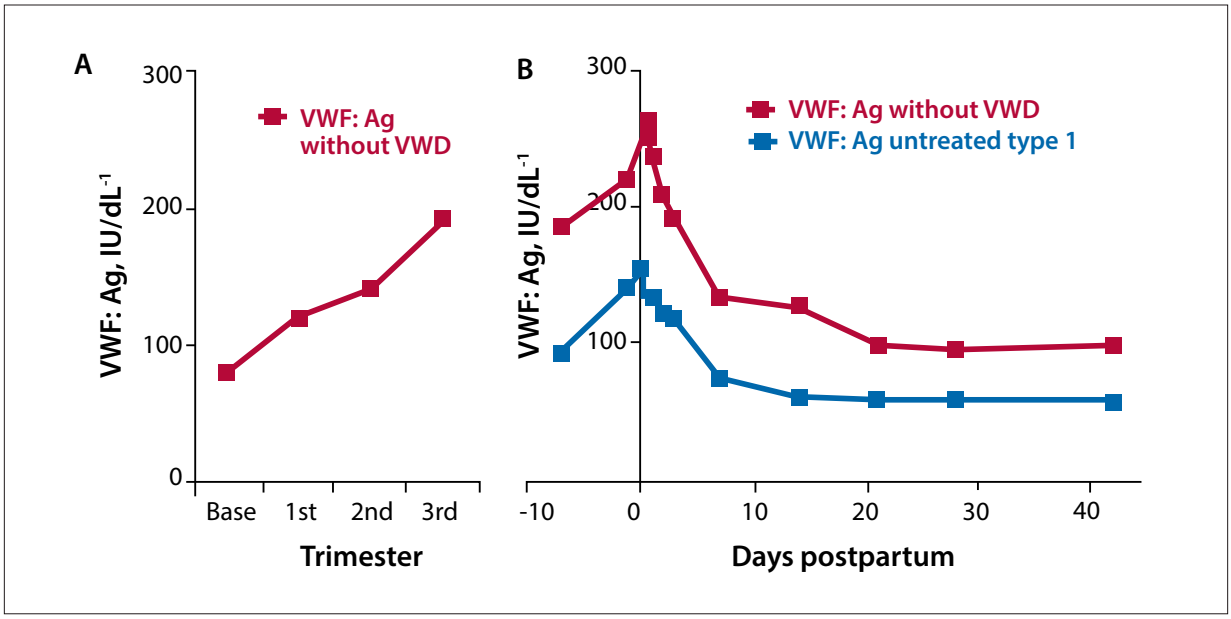

Figure. Change in VWF antigen (VWF:Ag) levels during pregnancy in women with and without VWD. (A) Progressive increase in VWF:Ag levels in healthy pregnancy. (B) Marked rises in VWF:Ag levels during labor followed by rapid declines after delivery in healthy women (red) and in women with type 1 VWD (blue) determined not to require treatment by their providers.

VWD, von Willebrand disease; VWF, von Willebrand factor.

Adapted from Drury-Stewart DN et al. *PLoS One*. 2014;9(11):e112935 (A) and James AH et al. *Haemophilia*. 2015;21(1):81-87 (B).

late in the pregnancy the levels are 250% higher than they were before the pregnancy. The levels begin to fall precipitously in the first hours and days after delivery of the placenta; they are close to baseline at 1 week after delivery and have returned to baseline by 6 weeks after delivery. We consider a 6-week blood draw to be equivalent to a nonpregnant blood draw.

Levels of VWF and factor VIII also increase during pregnancy in most women with type 1 VWD and some women with type 2 VWD, which allows them to withstand some hemostatic challenges during pregnancy. Although these proteins may reach levels that are considered normal in women who are not pregnant, they are still far lower than the levels seen in pregnant women without VWD.

Levels of VWF and factor VIII do not increase during pregnancy in women with type 3 VWD and most women with type 2 VWD. Evidence indicates that postpartum bleeding is greater in these women than in other women, even if they have received what seems to be adequate VWD prophylaxis.

H&O How does VWD affect pregnancy?

JJ Most women with VWD do well during pregnancy. Even women with type 3 VWD can have normal and otherwise healthy pregnancies. Some women have vaginal spotting or bleeding that is a little worse because of their VWD but is not caused by the disease. The typical increase in the levels of VWF seen in most women with VWD during pregnancy seems to be adequate for the administration of epidural or spinal anesthesia.

Childbirth and the postpartum period remains a hemostatic challenge, however. Even when pregnant women with VWD have levels of VWF that are considered normal for women who are not pregnant, they still have more postpartum bleeding than patients without VWD. Why should this be, when the VWF levels appear to be sufficient to provide good hemostasis? One possibility is that in the case of postpartum bleeding, a higher level of VWF than normal nonpregnant levels is required to achieve hemostasis. Another possibility is that our laboratory tests do not measure all the properties of VWF that play a role in hemostasis. More research is required. Regardless of the cause, however, the hospital staff must be aware that these patients are at increased risk for postpartum hemorrhage.

Another concern for women with VWD is that their iron levels may have been slightly low before pregnancy, so they are more likely to become anemic during pregnancy. The physician should make sure that the patient's iron level remains normal.

H&O What is the treatment approach for women with VWD who are pregnant?

JJ A woman with VWD who becomes pregnant requires care by a multidisciplinary team. An important step is putting all these team members in place early on: a hematologist, a high-risk obstetrician or one who is experienced in managing patients with a bleeding disorder, an anesthesiologist, and a neonatologist. The hospital should also have a pediatric hematologist available in case one is needed for the newborn.

Routine laboratory testing should be done first at approximately 28 weeks' gestation and again at approximately 34 to 36 weeks' gestation. This schedule allows us to determine whether a patient's VWF levels are increasing during the pregnancy. Knowing the VWF levels will also inform treatment if a bleeding complication develops, so we want to have a recent value. We also use the most recent VWF value during the pregnancy to develop a written birth plan. The birth plan describes the bleeding prophylaxis that may be needed for the delivery and postpartum period, and the steps to take to treat episodes of bleeding. Everyone on the team receives a copy of this plan.

The delivery should take place in a hospital where all is available that is required to manage potential complications if significant bleeding develops. This encompasses the expertise of an obstetrician, anesthesiologist, and neonatologist, along with access to resources such as a pharmacy and a blood bank. The facility must be able to care for a bleeding emergency in either the mother or the neonate. Some women wish to have a home birth, but this is contraindicated for patients with a bleeding disorder.

As I mentioned earlier, women with VWD have the option of neuraxial anesthesia—either epidural or spinal—if their VWF levels are normal or corrected with treatment. We recommend avoiding instrumentation when possible, but the route of delivery, vaginal or cesarean, is dictated by obstetric considerations alone.

Women with type 1 VWD typically do not require bleeding prophylaxis at the time of delivery, but we use an antifibrinolytic agent—usually tranexamic acid but sometimes aminocaproic acid—to provide postpartum prophylaxis. Some patients with type 1 VWD and most patients with type 2 or 3 VWD require VWF replacement therapy with either plasma-derived or recombinant VWF before delivery, and VWF replacement plus an antifibrinolytic for bleeding prophylaxis in the postpartum period. A longer period of prophylaxis is required after a cesarean delivery than after a vaginal delivery.

It is important to remain focused on the mother after delivery because it is easy to underestimate excessive postpartum bleeding or dismiss it as normal. If the patient tells a nurse about bleeding in the postpartum period, we want the nurse to inform the obstetrician and the hematologist. We also want the patient to call her physician about any bleeding after she has returned home. Good communication is essential.

H&O What are the risks to the infant?

JJ The chance that the baby will inherit the mother's bleeding disorder is 50% provided the father is unaffected, but this information has no bearing on the management of the pregnancy or delivery. There is no evidence that we should change, for example, the route of delivery depending on whether the child is affected. We do recommend avoiding instrumentation that could cause trauma to the mother or baby. We also want the neonatologist to be aware of the mother's condition so that the infant can be examined early for any signs of bleeding. However, most of the babies do very well and do not require testing for VWD until later in childhood. The babies who must be evaluated immediately by a pediatric hematologist are those who have signs of bleeding, are premature, or require a procedure.

Disclosure

Dr Johnsen has consulted for CSL Behring and Octapharma.

Suggested Readings

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