

VON WILLEBRAND FACTOR AND VON WILLEBRAND DISEASE IN PREGNANCY – A MANAGEABLE CHALLENGE

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Abstract

Repeated vaginal bleeding is a common complaint in outpatient obstetrical practice. Traditionally, it is treated with progesterone, without making an accurate etiological diagnosis. Hemorrhage during labor, delivery or postpartum period are considered obstetrical emergencies. Von Willebrand disease is one of the frequent causes for hereditary bleeding disorders; the diagnosis during pregnancy can be difficult due to physiological hematological changes. The aim of this study was to review the diagnostic criteria of von Willebrand disease and to recommend optimal management during pregnancy, delivery and postpartum period. The triad: family bleeding history, personal backgrounds of hemorrhage and easily appearing bruises after small trauma are suggestive for von Willebrand disease. However, the proper diagnosis is based on laboratory tests which consist of: von Willebrand-ristocetin cofactor activity, von Willebrand factor antigen, and factor VIII. In order to obtain optimal treatment outcomes, a multidisciplinary approach must include a hematologist as well. A prophylactic treatment with Haemate P® (CSL Behring, Marburg, Germany) is recommended in order to prevent any unwanted hemorrhagic events.

Rezumat : Factorul von Willebrand si boala von Willebrand in sarcina- o mare provocare

In practica curenta, sangerarea vaginala repetata este un simptom comun. De obicei, se trateaza cu progestative si diagnosticul etiologic nu se stabileste intotdeauna. Hemoragia in timpul travaliului, nasterii si in perioada lauziei sunt considerate urgente obstetricale. Boala von Willebrand este una dintre cele mai frecvente cauze ereditare de patologie hemoragica; in timpul sarcinii, datorita modificarilor hematologice fiziologice, diagnosticarea acesteia poate fi dificila. Scopul studiului a fost sa revedem criteriile de diagnostic ale bolii von Willebrand si sa recomandam o conduita optima in timpul supravegherii sarcinii, al nasterii si in perioada de lauzie. Triada: istoric familial de sangerare, istoric personal de hemoragii, aparitia echimozelor dupa traumatisme minore sugereaza boala von Willebrand. Diagnosticul este stabilit prin teste specifice de laborator precum: activitatea cofactorului von Willebrand la ristocetina, antigenul factorului von Willebrand, factorul VIII. O abordare multidisciplinara in care exista si medicul hematolog va asigura tratamentul optim. De fiecare data, pentru prevenirea hemoragiilor se va administra tratament cu Haemate P® (CSL Behring, Marburg, Germany).

Cuvinte cheie : boala von Willebrand , factorul von Willebrand, sarcina, Haemate P, hemoragie

Introduction

Von Willebrand disease (vWD) is the most frequent hereditary bleeding disorder with a prevalence of 1,3% in general population [1]. Its association with pregnancy is not common. However, isolated cases have been reported during pregnancy and after a postpartum hemorrhage episode with unexplained cause [2]. vWD is an autosomal inherited congenital pathology defined by either a quantitative or a qualitative deficit of von Willebrand Factor (vWF). vWF is a glycoprotein critical for proper platelet adhesion and protection against coagulant factor degradation. vWF is found in endothelial cells

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and megakaryocytes [3]. The abnormal activity of vWF is associated with mutation of vWF gene, located on the p arm of chromosome 12 (position 13.31) [4]. This can produce a several of clinical and laboratory phenotypes [5].

The aim of this study was to review the diagnostic criteria of vWD and to recommended optimal management of this pathology during pregnancy and postpartum period; the diagnosis has been established preconceptional or has been suspected during gestation.

Von Willebrand disease diagnosed before pregnancy

Despite the fact that this pathology affects both women and men, women are more symptomatic due to heavy menstrual bleeding or hemorrhagic episodes during delivery or postpartum period. When facing the triad consisted of family bleeding history, personal backgrounds of hemorrhage and easily appearing bruises after small trauma, further investigations are mandatory, including vWD diagnosis.

The most reported clinical symptoms of vWD are: heavy menstrual bleeding (74–92%) [6], epistaxis (38–63%), gingival bleeding (26–35%), bleeding after dental extraction (29–52%), bleeding from minor cuts or abrasions (36%), postoperative bleeding (20–28%), gastrointestinal bleeding (14%), and joint bleeding (6–8%) [7].

Types of von Willebrand Disease [2]

vWD is divided into 3 major categories: type 1, 2 and 3; type 2 being itself divided into several subcategories : type 2A, 2B, 2N, 2M.

Type 1 is the most common and is characterized by a quantitative deficit of vWF or

abnormally fast removal of vWF from the blood; however structurally vWF is normal. People with vWD type 1 might be asymptomatic – no need for treatment at all – or can present mild bleeding episodes.

Type 2 is less common than type 1 but more frequent than type 3 and is characterized by an abnormal structure of vWF. Frequently the symptoms are mild without the need for treatment.

Type 2A is the most common subtype; in this case the platelets do not bind together with the vWF. Type 2B is the second most common subtype defined by a low thrombocytes count.

Type 2N is rare and it is defined by low levels of factor VIII which can misdiagnose it for hemophilia.

Type 2M is extremely rare.

Type 3 is very rare and it is the most severe form – characterized by no detectable quantities of vWF leading to severe/lethal hemorrhages. Thus we always administer treatment in these cases.

Laboratory tests in vWD diagnosis

Providing a proper diagnosis it is essential especially if the patient intends to have a child, as pregnancy not only covers up a bleeding disorder but correct treatment will lead to a safe delivery with no hemorrhagic events.

The medical evaluation is not only consisted of a correct anamnesis including any personal al family bleeding history – epistaxis, easily appearing bruises, transfusions but also specific blood tests (Table 1).

Von Willebrand disease diagnosed during pregnancy.

It is critical to emphasize the significance of a proper preconceptional diagnosis, as the pregnancy

Table 1: Laboratory tests for vWD:

Specific Tests:	Concentration of vWF antigen (vWF:Ag)
	Ristocetin cofactor (RCoF) activity
	Factor VIII coagulant activity
Usual tests (modified in vWD):	Prothrombin time (PT)
	Activated partial thromboplastin time (aPTT)

itself is a protrombotic factor that can cover up an inherited bleeding disorder. Pregnancy represents a specific protrombotic physiological condition. The maternal organism adapts in order to confront massive bleeding during delivery and postpartum period. This hypercoagulability is generated by the endothelial activation, increased liver synthesis of coagulation factors, and decreased activity of coagulation inhibitors and fibrinolysis.

During pregnancy both vWF and VIII levels increase, reaching the highest peak between 29 and 35 weeks' gestation [8, 9]. Thus most women will be asymptomatic during pregnancy with no need for treatment in vWD type 1 and the majority cases of type 2. However, due to the lack of vWF in type 3 this adjustment does not occur and prophylactic factor replacement therapy is mandatory [10]. After delivery the coagulation factors levels return to baseline in 7 to 21 days leading to delayed severe hemorrhages in postpartum period if prophylactic treatment is not administered at least 2 weeks after delivery [8, 11].

Management of Von Willebrand disease associated with pregnancy

In order to achieve optimal treatment outcomes, a multidisciplinary management approach is required. An obstetrician, a hematologist, an anesthetist and a geneticist should present the medical options including mode of delivery, prophylactic hemorrhagic treatment, pain releasing medication available and the risk for the new born to inherit this condition.

Medical options include providing exogenous vWF/FVIII concentrate (Haemate P500 - 500 IU human FVIII and 1200 IU human vWF) or raising endogenous vWF levels using desmopressin acetate (1-desamino-8-D-arginine vasopressin [DDAVP]) - a synthetic analogue of vasopressin that increases the plasma levels of vWF and factor VIII [12]. However, considering its side effects such as uterine contractions and hyponatraemia [13], the lack of response in type 2 and 3 of vWD [14] and it's relatively contraindication it type 2B, experts recommendations include replacement therapy in type 2B and 3 vWD and in type 1 or 2 vWD who have a

low react to DDAVP [16].

When repeated vaginal bleeding episodes during pregnancy raise attention and proper laboratory test follow, two different situations have been described.

Firstly, laboratory tests are within normal ranges, yet not excluding a bleeding pathology. The prophylactic treatment with VWF/FVII concentrate during delivery and postpartum period were recommended in order to avoid massive hemorrhage. As soon as the maternal organism normalizes its hormonal levels as well as the coagulation factors, repeated laboratory tests are endorsed.

In the second situation the correct vWD diagnose was established during pregnancy; the monitoring of pregnancy should include a hematologist as well. Management during pregnancy should include coagulation factor levels measurement at presentation, before any invasive procedure and in the third trimester before delivery. If below normal range, replacement therapy with vWF/FVIII concentrate (Haemate P500 - 500 IU human FVIII and 1200 IU human vWF) is compulsory [10, 16, 17]. Moreover, in vWD type 2B, thrombocytopenia can worsen during pregnancy and platelets transfusion is required.

Patients with vWD can have a safe vaginal delivery leaving a Caesarean section only for obstetrical indications [10, 16]. However it is recommended to normalize vWF and VIII levels as much as possible before delivery using replacement therapy thus avoiding any hemorrhagic event.

Operative vaginal deliveries by vacuum extraction or use of forceps are contraindicated [10, 16] because these maneuvers can lead to intracranial hemorrhage [18]. The likelihood that the new born inherit vWD is 50%.

The use of epidural analgesia is not contraindicated [10], but should only be considered if coagulation factor levels are within normal range (> 50 IU/dL); Epidural analgesia representing a high risk for spinal hematoma in these cases.

After delivery the coagulation factors levels return to baseline in 7 to 21 days leading to delayed severe hemorrhages in postpartum period if prophylactic treatment is not administered [8, 11].

The literature regarding vWD treatment in pregnancy is not extensive. A recent review analyzed 62 pregnancies, from 33 women with vWD. The results state that women are at a higher risk of postpartum hemorrhage as they age and if they deliver vaginal. Moreover they identified that a low third trimester VWF:RCo is one of the risk factors of postpartum bleeding [19].

In conclusion, we believed that during pregnancy vWD can be easily misdiagnosed ; the hyperestrogenism and the physiological increase of vWF, modifies routine laboratory tests. However repeated vaginal bleeding episodes should raise awareness and further proper investigations should follow. Furthermore, laboratory test can come out within normal ranges during pregnancy, thus after the postpartum period we recommend repeating the investigation. If proper diagnosis was established preconceptual, pursue the hematologist indications should lead to safety delivery with no hemorrhagic events encountered. However we strongly advocate for vaginal delivery in favor of delivery by Cesarean section.

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