CASE SERIES

Von Willebrand's Disease and Pregnancy: Case Series of a Rare Entity

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Abstract

Von Willebrand's disease is an inherited bleeding disorder, which perhaps can be a life-threatening emergency in pregnancy, delivery, and early puerperium, therefore, early diagnosis and minimizing or controlling blood loss is the main aim. It is a condition where the body is either in deficiency of factor VIII or its binding protein, which leads to increased tendencies of bleeding. Here, we will be discussing four cases, highlighting their diagnosis and clinical management. Our study aims to present different clinical scenarios where pregnant women with von Willebrand's disease presented to our clinical setup, citing the various complications during the peripartum period and their management to improve their obstetric outcome.

Keywords: Factor VIII deficiency, Von Willebrand disease, Von Willebrand factor.

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Introduction

Pregnancy is physiologically a hypercoagulable state. Pregnant women, irrespective of any disease, are at high risk of hemorrhage. To help prevent it, clotting factors increase, whereas anticoagulants decrease physiologically in the human body. Von Willebrand disease (VWD) is one of the commonly inherited bleeding disorders. Following any vascular injury, von Willebrand factor is released, which requires adhesion of the platelets to the subendothelium.

The subtypes include partial (type-1) or total (type-3) deficiency of von Willebrand factor (VWF) levels and qualitative defects of VWF (type-2).[1] It is generally diagnosed with symptoms of epistaxis, easy bruisability, heavy menstrual bleeding, and treatment is based on the severity of the symptoms, mostly symptomatic.

Case Description

Case 1

A 23-year-old primigravida, a diagnosed case of von Willebrand's disease and gestational diabetes mellitus, a registered antenatal case, was admitted during the third trimester for safe confinement at KEM hospital. The hematologist's opinion was taken, and the delivery plan was devised. A weekly prophylactic dose of factor VIII (20 IU/kg body wt) was transfused from the beginning of the third trimester. The patient went into labor spontaneously and delivered vaginally with episiotomy, a female child of 3.2 kg. Factor VIII (80%) was transfused during the peridelivery period. About 4 hours later, episiotomy swelling was noted. The patient was taken up for vaginal exploration after transfusion of factor VIII 2500 IU (100%). Intraoperatively, 8 × 5 × 5 cm hematoma was observed, and approximately 350 gm of blood clots were evacuated from the episiotomy site. Two pints of PRBC were transfused, resuturing of the episiotomy site was done, and hemostasis was confirmed. Post delivery, the patient received 60% factor VIII correction daily for 3 days along with tranexamic acid. Mother and baby were discharged on day 9 of delivery in a healthy state.

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Case 2

A 22-year-old G3P1L1MTP1, a known case of von Willebrand's disease 2N, was admitted to the emergency room of KEM hospital in early labor. Her antenatal period was unremarkable. Previously, the patient had delivered vaginally, during which factor VIII correction was given. All routine investigations were done and were found to be within normal-range factor VIII C levels that were 10.5% of normal pooled plasma. The patient progressed into active labor spontaneously. As the patient progressed to the second stage of labor, factor VIII 2000 IU was transfused (80%) intravenously. The patient was taken up for emergency lower segment cesarean section in view of arrest of the second stage of labor after transfusing an additional 500 IU of factor VIII (total 100%). Intraoperatively, 3 pints of PRBC were transfused to combat blood loss. Twelve hours post delivery, 1500 IU factor VIII (60%) was transfused twice daily for 2 days with twice-daily CBC monitoring. The postoperative period was uneventful. Mother and baby were discharged on day 9.

Case 3

A 32-year-old G2E1, a known case of combined factor V + VIII deficiency since 1998, registered antenatally at KEM Hospital.

The antenatal period was uneventful. At 38 weeks, on regular OPD visit, the patient was found to be in active labor. Factor VIII C levels were 14.4% of normal pooled plasma. The patient was admitted, and factor VIII (100%) was transfused along with 8 pints of fresh frozen plasma in the peridelivery period. She delivered a male child of 3.04 kg. Post delivery, the patient was transfused factor VIII (60%) on days 2 and 3, and factor VIII 500 IU twice a day on days 4, 5, 6. Mother and baby were discharged on day 9.

Case 4

A 28-year-old primigravida, a known case of von Willebrand's disease 2B, registered at KEM hospital. She was admitted for safe confinement at 34 weeks. VWF 2400 IU and factor VIII 1000 IU were transfused biweekly as prophylactic dose. At 36 weeks, the patient went into preterm labor and delivered vaginally. Peridelivery, she was transfused VWF 3600 IU and factor VIII 1500 IU. On day 2, the patient had an episode of postpartum hemorrhage, and was transfused with 100% correction along with 3 pints of packed red blood cells, following which the patient received 100% correction on days 3, 4, and 5. The patient was discharged on day 9. The patient was readmitted on day 28 with postpartum hemorrhage, and was conservatively managed. She was transfused with 3 pints of packed red blood cells, VWF 3600 IU, and factor VIII 1500 IU. Correction was given for 3 days consecutively, and the patient recovered and was hemodynamically stable and discharged on day 39.

Discussion

Pregnancy care in a case of von Willebrand's disease is a bothersome obstacle. Von Willebrand's disease is a hereditary hematological disorder due to qualitative or quantitative deficiency of factor VIII. The varying pattern observed during pregnancy warrants a diligent examination of pregnant women with VWD to plan appropriate treatment at the time of delivery. However, there are also events during pregnancy like amniocentesis, vaginal bleeding due to abruption, and sudden abortion that may require urgent hemostatic treatment to prevent bleeding.

There are three variants of VWD:
It is the most common form of VWD with low levels of VWF.

- *Type 1*
  Approximately, 85% of affected people have type 1. VWF levels are usually 20–40%. Most of them go unnoticed during their lifetime.

- *Type 2 (Qualitative Deficiency)*
  Under this type, despite producing normal levels of factor, qualitative defects are seen. Type 2 is further classified within four subtypes – 2A, 2B, 2M, and 2N.
  - In type 2A, the ability to combine and form large molecules of VWF is reduced, thereby smaller multimers in circulation.
  - In type 2B, the defective VWF attaches to platelets when there is no injury and the body removes these platelets leading to decreased circulatory levels of platelets and factor VIII.
  - In type 2M, the VWF does not adhere to the membrane of the platelets, which decreases the platelets' ability to form a clot. Circulatory levels of factor are within normal limits
  - In type 2N, the VWF attaches to the platelets as per normal.

However, the VWF does not attach to another protein, factor VIII is needed for blood to clot.

- *Type 3*
  It is the most critical form of VWD in which circulatory levels of factor VIII and VWF are almost depleted. It is an infrequent type of VWD amounting to an incidence of 3%.[1]

Pregnancy is a prothrombotic state. Hemostatic factors, which include factor VII, X, fibrinogen, and plasminogen activator inhibitor type 1 increase, while free protein S decreases. VWF and FVIII increase remarkably during pregnancy in normal women, reaching their maximum during the third trimester. These are the adaptive changes that the body undergoes to face obstetric hematological challenges. Despite these, numerous obstetric complications may arise causing bleeding.

Clinical Presentation

The major presenting signs of VWD, which should raise suspicion are:

- Recurrent nosebleeds without injury (spontaneous) lasting more than 10 minutes and need treatment to stop the bleeding from occurring multiple times a year.
- Easy bruisablility with no trauma or injury.
- Heavy menstrual bleeding lasting much longer than usual in women leads to anemia.[2]

A detailed and thorough history and clinical examination are essential for any patient with a suspected bleeding disorder. Screening of all women with the abovementioned symptoms and laboratory testing must be carried out. Occasionally, repeat testing may be essential for arriving at an accurate opinion. Basic tests performed in a case of suspected hematological condition are a complete blood count, activated partial thromboplastin time, prothrombin time, thrombin time, and fibrinogen level. Patients with abnormal results typically undergo further evaluation. Under laboratory levels of factor VIII, VWF antigen assay is carried out.[3]

Treatment

Pregnant women with VWD are at higher risk of bleeding during delivery. Hence, treatment plans should be devised from conception onward. Instrumental delivery should be less preferred as it increases the chances of bleeding. Infusion with desmopressin should be administered before pregnancy for every woman with VWD. Other approaches using FVIII/VWF concentrates are also used. About 40–60 IU/kg VWF is transfused peridelivery and repeated daily for 3 days and subsequently oral antifibrinolytics for 1 week.

Women with type 3 VWD do not show any elevation of FVIII and VWF during pregnancy due to inherent deficiency. Thus, VWF/FVIII concentrates would be required during pregnancy and peripartum period. Some women with type 3 VWD may be on prophylactic VWF concentrate before pregnancy, and this is usually carried over throughout the pregnancy and titrated as per weight gain.[4] Replacement therapy should be continued for 1 week to maintain FVIII:C (and possibly VWF) above 50 U/dL. FVIII and VWF fall to minimum levels. Immediately, postpartum and thus oral antifibrinolytic agents can be given during this period to prevent delayed postpartum hemorrhage. However, if significant delayed bleeding occurs, treatment with desmopressin or FVIII/VWF concentrates is required.[3]

Conclusion

About 1% of the population is affected by von Willebrand disease. Women with von Willebrand disease are in peril for life-threatening

bleeding post delivery. Close surveillance is always advisable. Pregnancy is a hypercoagulable state within itself. Deficiency of any clotting factor poses a hemostatic challenge that necessitates undivided attention and care throughout pregnancy and post delivery through a multidisciplinary approach.[5,6]

The presence of VWD does not warrant cesarean section. Additionally, antifibrinolytics play a pivotal role in the treatment and prevention of excessive bleeding during puerperium.[6]

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