Open Access Case Report

Successful Pregnancies in a Case of Severe (Type 3) von Willebrand Disease

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Introduction

Given the wide heterogeneity of phenotypes and the underlying pathophysiological mechanisms associated with the disorder, pregnancy and delivery in VWD represents a significant clinical challenge. The variable pattern of changes observed during pregnancy in von willebrand factor (VWF) and factor VIII (F-VIII), the protein carried by VWF, prompts a careful evaluation of pregnant women with VWD to plan the most appropriate treatment at the time of parturition. [1]Women with von Willebrand Disease (VWD) are at an increased risk of bleeding and other complications during pregnancy and childbirth.[2,3]

Women with inherited bleeding disorders, including VWD, are concerned about their bleeding and possible bleeding complications. All these leads to upfront efforts to give this cohort a safe reproductive fruition. Last 20 years have witnessed progression in understanding diagnosis, and treating complications in women with VWD.[1-6]

Case Report

A 34 years old lady, had history of repeated episodes of menorrhagia, since menarche and frequent episodes of mucocutaneous bleeds. She was diagnosed as a case of von Willebrand Disease Type-3 (VWD – Type 3) (Table I).

At multiple times she was treated with inj VWF 1200/500 IU IV, Fresh Frozen Plasma (FFP), Capsule Transaminand Hormonal therapy. She got married. After Stopping Contraceptive pills, subsequently she conceived after 2 and half months. Patient was given reassurance and anti-natal check-up /per month was done regularly. She delivered a healthy baby girl, weight 3.2kg in Benazir Bhutto Hospital, Rawalpindi. After 3 weeks of delivery, she had an episode of Severe vaginal bleeding (Secondary Post Partum Haemorrhage; PPH), for which she was treated with injections VWF 1200/500 IU I/V (05 injections) and capsule Transamin 1gm thrice daily, she became stable and discharged from the hospital.

Table I: von Willebrand Disease – Laboratory Findings.

Laboratory Parameter	Result
Bleeding Time	Prolonged
Prothrombin Time	Normal
Activated Partial Thromboplastin Time	Prolonged
Platelet count	Normal
Mixing Studies	Not corrected by aged serum;corrected by adsorbed plasma
Platelet Aggregation Studies	Absent aggregation with Ristoceitin; Normal aggregation with rest of agonists
Factor –VIII level	11 IU/dl
VWF Antigen	Undetectable

After two years she conceived again. She had regular anti-natal check-ups. Gave birth to a baby boy in Haripur (Home delivery). After three weeks she had severe vaginal bleeding (Secondary Post Partum Haemorrhage; PPH). She was brought to Haemophilia Treatment Center (HTC), Rawalpindi. She was admitted in Benazir Bhutto Hospital. She received two pints of red blood cells concentrates, three doses VWF (1200/500IU) and capsule Transamin 1 gram thrice daily. Her bleeding subsided. At both deliveries children did not have any childbirth related trauma.

Discussion

VWD is caused by deficiency or dysfunction of von Willebrand Factor (VWF), a plasma protein that mediates the initial adhesion of platelets at sites of vascular injury and binds and stabilizes blood clotting factor VIII in the circulation. As such, defects in VWF can lead to bleeding because of impaired platelet adhesion or reduced F-VIII concentration.[2] VWD is classified into three major categories. In Type-1 there is partial quantitative deficiency of VWF. Type – 2, qualitative defect, is further divided into four subtypes (2A,2B, 2M,2N), according to different impairments in the form and/or function of VWF.Type-3 corresponds to an almost total absence of VWF. Type 1 and 2 are autosomal dominant, while typ-3 is autosomal recessive. World over type -1 is the commonest type. In our country, due to consanguineous / family marriages the autosomal recessive typ-3 is most common.[4-9] History of consanguineous marriage is found in majority of patients with VWD in our patients .[7,15]

The diagnosis of higher number of patients of type-3 VWD can be ascribed to that fact that these patients are severely affected and symptomatic. On the other hand, patients with type-1 VWD had mild symptoms, as a result lesser numbers sought for medical advice leading to underdiagnosis of mild type-1 VWD. These milder forms are often missed out on diagnosis or may not be detected at all as screening tests may be normal.[14]

Ahmed S et al (2019) and Naveed MA et al (2022) reported that in type-3 patients splice site mutations and truncating mutations can be held responsible for a more severe disease.[5,16] Women with basal von Willbrand antigen (VW Ag) levels less than 20U/dl usually have a lesser increase, since most of these women carry DNA variants associated with increased VWF clearance or decreased synthesis and secretion or are compound heterozygous for different VWF variants which prevent the achievement of satisfactory hemostatic level. [10-15]

Although VWD occurs equally in males and females, women are at a higher risk of being effected, mostly because of bleeding challenges associated with menstruation, pregnancy and childbirth.[2] Women with VWD should have well characterized their type and treatment modalities at the start of pregnancy. Due to high complexity of VWD, a whole panel of laboratory tests is required to diagnose and classify VWD, an essential step for the subsequent clinical management. [14,19] Identifying the type of congenital bleeding disorder and knowing its inheritance pattern is crucial during counseling prior to conception and in preparation for delivery. [1,3]

During pregnancy, many changes in haemostasis occur that results in a hypercoagulable state. In pregnancy, levels of several hemostatic factors increase, including factor F-VIII, VWF, VII, X, fibrinogen and plasminogen activator inhibitor type -1. The levels of F-VIII and VWF starts increasing in the second trimester and peak during third trimester. These increases depend on the type and sub-type of VWD. Women with typ-1 and type-2 VWD usually achieve normal VWF and F-VIII levels at the end of pregnancy, but these levels remain unchanged in women with type-3VWD during pregnancy. F-VIII and VWF levels decrease rapidly after delivery in women with VWD, approaching baseline after1 week and reaching baseline after 3 weeks. Consequently, women with VWD may be at risk of postpartum haemorrhage .[12,13,17]

Women with VWD are at risk from a variety of bleeding complications during pregnancy, as a result of invasive prenatal diagnostic and monitoring procedures, spontaneous or elective abortions and hemostatic challenge of pregnancy.[17] Infant is at potential risk of serious complications, e.g., scalp and intracranial haemorrhage during childbirth and instrumental deliveries. It is recommended that delivery should be achieved in least traumatic manner.[2]

Women with inherited bleeding disorders, including VWD, have a high incidence of post partumhaemorrhage (PPH). Primary post-partum haemorrhage is defined as a loss of more than 500 ml blood loss within 24 hours after birth and secondary post-partum haemorrhage is defined as bleeding that exceeds normal lochial loss 24 hours to weeks after delivery.[2] In literature the incidence of secondary post-partum haemorrhage in women with VWD varies from 20% to 28%.[2,16] In a substantial number of cases diagnosis of VWD is usually unknown prior to presentation with PPH.[17]

SladicM et all (2022) compared women with VWD with women without VWD. They found that women with VWD were not more likely to have cervical cerclage, anaemia or thrombocytopenia than women without VWD. There were no cases of intrauterine fetal growth restriction in study group. Women with VWD were not more likely to experience vaginal bleeding in first and second trimester

of pregnancy, but were five times more likely to experience vaginal bleeding in third trimester of pregnancy. The incidence of cesarean sections was similar in both groups. Women with VWD were more likely to experience primary post-partum haemorrhage (7.7%), than without VWD (2.2%). However, women with VWD were more likely to experience childbirth trauma-related bleeding, primary post-partum haemorrhage and require blood transfusion after child birth. They did not observe any case of still birth or early neonatal death in women with VWD.[2]

Levels of VWF and F-VIII remain low throughout pregnancy in women with type-3 VWD. In all types of VWD, due to unpredictable increase in factors levels, frequent monitoring with at least one level obtained 28-34 weeks of gestation, helps in determining the treatment and delivery plans.[3]

Different treatment options may be used during delivery or in the postpartum period, depending on type of VWD and risk of bleeding.[12]Caesarean section should be reserved only for the usual obstetrical indications. Replacement therapy should be prolonged up to 7 days to maintain F-VIII:C (and possibly VWF) level more than 50 U/dl.[1] Anesthetists are often reluctant to administer epidural anesthesia, in women with inherited bleeding disorders, due to risk of spinal hematoma .[22]

Infants with VWD are at risk from intracranial haemorrhage and from scalp hematoma during labour and vaginal delivery, especially with the use of invasive monitoring techniques, forceps or other instrumentations.[22] Bleeding complications in the new born are raised in particular with some type-2 and type-3 patients.[3]

Conclusion

1. An accurate diagnosis and management of bleeding disorder in pregnancy must take into consideration the risks to the mother and fetus with individualized planning and care by a team of specialists in a tertiary care center, these women can, in their majority, carry a pregnancy to term and deliver healthy newborn.
2. There is a higher incidence of particular complications during childbirth and the postpartum period in women with VWD, such as primary and secondary postpartum haemorrhage, childbirth trauma –related bleeding and receiving blood transfusion within the first 24 hours after child birth.
3. A proper liaison with Haemophlia Treatment Center (HTC) ensures successful pregnancy outcome and adequate management of post-delivery complications, like PPH.
4. Increased awareness, better understanding of this disorder and strong interdisciplinary collaboration are of utmost importance in achieving optimal outcomes and minimizing maternal and neonatal complications.

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