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# Management of a Pregnant Patient with Platelet Type Von Willebrand Disorder: Case Report and Review of Literature

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## ABSTRACT

**Introduction:** Platelet type Von Willebrand disorder (PT - VWD) is an autosomal bleeding syndrome induced by an irregular glycoprotein Ib protein function that results in platelets that are hyperresponsive. While this condition seems to be well described due to this single molecular defect, diagnosis and management can be difficult. It usually has an autosomal dominant pattern of inheritance. PT-VWD is the least popular among all other VWDs, and only fewer than 50 patients have been reported in the literature.

**Objective:** To investigate the impact of platelet transfusion and also to assess the bleeding risk in the management of platelet type vWD patients, especially pregnant women, and therefore, a lack of data on the most competent method for assessing bleeding risk and supervising hemostasis in these patients.

**Methods:** The participant was a 27-year-old female with platelet type vWD along with hypothyroid, who came with 6 weeks of gestation for expectant management of her pregnancy.

**Results:** Since there were no bleeding risks, the platelet (SDP) was transfused before delivery. A healthy female baby was delivered with no further complications and the patient was comfortable with stable vitals.

**Conclusion:** This case report highlights the significance of multiple lab investigations in the diagnosis of the different forms of vWD, complications in management decisions, avoiding bleeding in such patients. This case study also evokes interest in the utility of platelet transfusions in PT -vWD. Our patient had an uneventful pregnancy with no bleeding complications and delivered a healthy female child.

**Keywords:** PT-vWD, Von Willebrand Factor, GP1bA, Factor VIII, Type 2B vWD, Bleeding disorder.

## INTRODUCTION

VWF is a large multimeric glycoprotein that plays two important roles in primary hemostasis: it forms a bridge between platelets at vascular injury sites for normal platelet adhesion, and it forms a bridge between platelets at vascular injury sites for normal platelet adhesion. The most common inherited bleeding disorder that results from the deficiency or abnormal function of von Willebrand factor (vWF) neces-

sary for platelet adhesion and aggregation is von Willebrand disease (VWD).<sup>1,4</sup> It also binds to and stabilizes Factor VIII, which is essential for secondary hemostasis.<sup>2,4</sup> This disease has three different subtypes. Quantitative and qualitative (Type 2-2A,2B,2M,2N) deficiencies (Type 2-2A,2B,2M,2N) can be attributed to it. <sup>3</sup>The prevalence rate of type 1 vWD is about 42.5 per cent, followed by 30 per cent of type 3 and 27.5 per cent of type 2 [type 2A (9.52 per cent), type 2B (13.18 per cent), type 2M (1.2 per cent), type 2N (3.6 per

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cent)].<sup>5,6</sup> However, PT-vWD is also an autosomal dominant condition caused by vWF receptor gain-of-function mutation on platelets and is similar to vWD type 2B caused by vWD. There is an abnormally enhanced binding of normal vWF to an abnormal platelet glycoprotein Iba (GP1ba) receptor due to a mutation in the GP Iba gene (GP1bA) to chromosome 17 in PT-vWD.<sup>3</sup> There was no systematic study of the prevalence of PT-vWD. Typically, patients with this condition undergo platelet transfusion therapy.<sup>2</sup> The use of cryoprecipitate in PT-VWD continues to be controversial, with increased thrombocytopenia reported in these products. The management of a pregnant woman admitted to the haematology department with platelet type vWD is identified in this case study, with its diagnostic and therapeutic difficulties.

## CASE DESCRIPTION

**Subject:** A 27-year-old woman diagnosed with platelet type vWD from outside presented to our hospital with 6 weeks of gestation for expectant management of her pregnancy. In the past, in her first pregnancy, she had a history of early abortions. She also gave a history of simple disability and one episode of trauma-following sustained gum bleeding. No history of menorrhagia or any other signs of bleeding is present. She was on substitute thyroxine for hypothyroidism. She was born to non-consanguineous parents and a father with a family history of platelet type vWD. Also, her paternal uncle had low vWF levels but was asymptomatic. A prothrombin time (PT) of 9.8 secs, triggered partial thromboplastin time (aPTT) of 36.8 secs, FVIII: C of 32.3 per cent, vWF: RCo of 13.6 per cent, vWF: Ag of 23.4 u/dl, vWF: RCo/vWF Ag ratio of <0.6 and platelet count of  $13 \times 10^3/\text{mm}^3$  was seen in the initial hemostatic workup performed outside. There was an irregular aggregation response to low-dose ristocetin (0.5 mg/ml) in platelet aggregation studies. In mixing experiments, low-dose ristocetin response was seen when patient platelets were mixed with control plasma, while no response was seen when patient plasma was mixed with control platelets.

### Objective examination

Initial hemostatic tests at 6 weeks of gestation showed 13 seconds of prothrombin time (PT), 36.7 seconds of triggered partial thromboplastin time (aPTT), 65 per cent of FVIII: C, 20 per cent of vWF: RCo, 36 per cent of vWF: Ag, <0.6 of vWF: RCo/vWF Ag ratio and  $56 \times 10^3/\text{mm}^3$  of platelet count. There was an irregular aggregation response to low-dose ristocetin (0.5 mg/ml) in platelet aggregation studies. The discrepancy with previous studies has been due to physiological improvements in pregnancy coagulation factors. The platelet count was found at 15 weeks of gestation to be  $46 \times 10^3/\text{mm}^3$ . **Table 1.** By the end of 2<sup>nd</sup> trimester, the platelet count dropped to  $29 \times 10^3/\text{mm}^3$ , however, there was no active bleeding.

## Investigations

Till the third trimester, the patient was managed conservatively with monitoring of platelet counts and was on oral iron, calcium, and thyroxine therapy. The platelet count was about  $45 \times 10^3/\text{mm}^3$  by 33 weeks of gestation. At 34 weeks gestation, the ultrasound revealed a posteriorly located placenta, and a cesarean section was recommended because of the risk of bleeding. The Patient was admitted for elective surgery at 37 weeks of gestation.

### On observation

Pre-surgery hemostatic plan was made with a target of >50% Factor VIII and vWAg levels, a normal Thromboelastogram, RiCoF>50%, and a platelet count of  $50 \times 10^3/\text{mm}^3$  with vWAg rich clotting factor concentrate infusion and platelet transfusions. In the preoperative period, her coagulation parameters were found to be normal with FVIII: C of 174%, vWF: Ag of 144% and RiCoF activity of 94%, and platelet count  $95 \times 10^3/\text{mm}^3$ . PT and aPTT were 14s and 32s respectively **table 1.** Also, she hadn't experienced any bleeding complications. However, no platelet transfusions or plasma or VWfactor were required as the patient was found to be normal. Desmopressin was not given to the patient.

### Outcome measures

The patient was taken up for elective LSCS under general anaesthesia. Two units of Single Donor Platelets (SDP) were transfused intraoperatively. A term lives female baby of 3.335 kg was delivered. After delivery, the patient was comfortable with stable vitals. Since the pre-operative investigations were normal, vWF concentrates were not administered before and during the delivery. The post-partum period was quite uneventful and no abnormal bleeding was reported. The child cried immediately after birth and did not have any bleeding complications.

## DISCUSSION

Since the diagnosis of platelet type von Willebrand disease (PT-VWD) had been identified before pregnancy, there was no diagnostic difficulty in separating it from type 2B VWD in our patient. Because of the substantial drop in platelet count with increasing gestation, deciding when to institute platelet transfusion and whether to give cryoprecipitate, as well as when to induce labour, were the challenges in this case. The condition's rarity, as well as the relative lack of experience in its management, made it more difficult. A good outcome for both the patient and the neonate was achieved with the participation of multi-disciplinary senior team members. Since there is a high risk of thrombocytopenia in these patients, their platelet count should always be controlled, and platelet transfusion is preferred.

The most common hereditary bleeding condition is Von Willebrand disease (VWD). Despite advances in our understanding of the pathophysiology of VWD, diagnosing the disease remains challenging due to uncertainty about the relationship between laboratory assays and function in vivo.

The association between the adhesive protein von Willebrand factor (VWF) and the platelets is important in the initiation and progression of thrombus formation at vascular damage sites.<sup>1</sup> VWF binds platelets via two major platelet receptors:

- The first, inside the protein complex of GPIb-IX, is glycoprotein Ib a (GP1bA gene). This relationship intervenes the adhesion of platelets and initial VWF tethering
- Integrin  $\alpha$ IIb $\beta$ 3 (GPIIb/IIIa) is the second platelet receptor; an interaction that is responsible for firmer attachment and further platelet arrest and activation triggered by more physiological stimuli such as ADP and thrombin, thus providing an ideal surface for a stable thrombus at the injury site.<sup>5</sup>

Three inherited bleeding disorders result from the irregular binding of vWF to GP1b. Gain-of-function phenotypes with enhanced binding affinities between the adhesive protein VWF and its receptor-ligand GP1b are two such disorders, type 2B von Willebrand disease and platelet-type von Willebrand disease.<sup>1,7</sup> **Table 2A** bleeding phenotype caused by loss-of-function GP1b gene mutations, Bernard-Soulier Syndrome (BSS) with thrombocytopenia, giant platelets and reduced RIPA (i.e. decreased RIPA).<sup>2,8</sup>

- a. Both represent gain-of-function mutations
- b. Both have autosomal dominant modes of inheritance
- c. Both the mutations result in increased binding of plasma vWF to its platelet receptor GP1b.
- d. They share common laboratory and clinical phenotype-
  - Usual clinical phenotypes involving excessive mucocutaneous bleeding involving simple bruising, frequent and extreme nosebleeds, menorrhagia, and excessive bleeding following a tooth extraction, tonsillectomy, and other surgical procedures
  - Bleeding becomes more apparent after the intake of aspirin or medications that have an antiplatelet function.
  - Loss of vWF high molecular weight multimers and characteristically enhanced RIPA (at 0.5 mg/mL or lower ristocetin concentrations), low or near-normal factor VIII levels, low or near-normal VWF antigen levels and generally low ristocetin cofactor activity are laboratories characteristics<sup>10</sup> **Table 2**
  - The platelet count may be normal, but there may be mild to moderate intermittent thrombocytopenia, and conditions like pregnancy, stress and infection can cause the condition to worsen.

However, it is essential to differentiate between the two disorders since there are subtle differences in the management of these disorders. They can be differentiated as follows

Laboratory discrimination between the two conditions may be an issue because basic baseline tests do not classify the disorders differently, and more complex testing methods such as the cryoprecipitate challenge test and the platelet mixing test are often incorrectly implemented.<sup>8,2</sup>

## CONCLUSION

To conclude, in a patient with platelet-type vWD, we have concisely defined the diagnosis, path, management, and outcome of pregnancy. For the management of such cases, the availability of tests such as vWF antigen, RiCoF activity, and thromboelastogram, together with serial platelet count measurements accompanied by sufficient blood product replacement, is important.<sup>11</sup> Because it shows the hemostatic complications of pregnancy, this rare case may be educational to many obstetricians and haematologists around the world. In this case, the importance of a multidisciplinary team approach was shown, resulting in a positive outcome for both the patient and the neonate. Some haematology experts believe that if platelet type von Willebrand disease is thoroughly studied, it may be discovered to be more widespread than current literature suggests.

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**Table 1: Maternal Laboratory Investigations during pregnancy**

Parameters	6 weeks	15 weeks	27 weeks	33 weeks	37weeks
PT (secs)	13	-	-	-	14
aPTT (secs)	36.7	-	-	-	32
FVIII:C (%)	65	-	-	-	174
vWF:RCo (%)	20	-	-	-	94
vWF:Ag (%)	36	-	-	-	144
vWF:RCo/vWF Ag ratio	<0.6	-	-	-	-
Platelet count	56x10 <sup>3</sup> /mm <sup>3</sup>	46x10 <sup>3</sup> /mm <sup>3</sup>	29x10 <sup>3</sup> /mm <sup>3</sup>	45x10 <sup>3</sup> /mm <sup>3</sup>	95 x 10 <sup>3</sup> /mm <sup>3</sup>

**Table 2: Differentiation of Platelet type and Type 2B Von Willebrand Disease<sup>10,11</sup>**

Platelet type- vWD	TYPE 2B vWD
<ul style="list-style-type: none"> <li>o Hyper-responsive platelets resulting from mutations in the GPIbA platelet gene on chromosome 17 are caused by PT-vWD<sup>9</sup></li> <li>o The affinity of an irregular platelet GPIb complex is increased in normal plasma VWF.</li> <li>o Increased response to low dose RIPA using platelets of the patient and normal plasma</li> </ul>	<ul style="list-style-type: none"> <li>o A functionally abnormal VWF molecule arising from chromosome 12 mutations in the vWF gene emerges from type 2B vWD.</li> <li>o Abnormal plasma vWF has a higher affinity for the normal platelet GPIbA complex.</li> <li>o Enhanced response using the patient's plasma and normal platelets to low dose RIPA</li> </ul>
<b>CRYOPRECIPITATE CHALLENGE TEST</b>	
<ul style="list-style-type: none"> <li>o Improved abnormal response to low-dose RIPA following mixing with the patient's cryoprecipitate platelets (source of normal vWF)<sup>10</sup></li> </ul>	<ul style="list-style-type: none"> <li>o Absent/normal response to low dose RIPA following mixing with the patient's cryoprecipitate platelets (source of normal vWF)</li> </ul>
<b>PLATELET MIXING TEST</b>	
<ul style="list-style-type: none"> <li>o After mixing plasma with normal platelets in the patient, Absent/normal low dose RIPA response</li> <li>o Investigation of specific GPIb gene mutations<sup>9,10</sup></li> <li>o Management involves platelet transfusions</li> </ul>	<ul style="list-style-type: none"> <li>o Increased abnormal reaction to low-dose RIPA after mixing with usual plasma platelets</li> <li>o Review of specific mutations in exon 28 of the vWF gene</li> <li>o Management requires plasma-derived VWF concentrates</li> </ul>