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Pregnancy with Von Willebrand's Disease: A Case Report

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Abstract: ***Women experience naturally occurring physiological events such as menstruation, pregnancy and childbirth that put them at risk of excessive bleeding even if they do not have a bleeding disorder. In this paper the authors review a case of pregnancy in the third trimester with a history of von Willebrand's disease where the patient does not routinely control medication and includes the latest theoretical studies in order to provide benefits in clinical practice at a later date. The patient with the initials KAE, aged 25 years with history of von Willebrand's disease since the age of 17 but was not seen frequently. On laboratory examination, a mild microcytic hypochromic anemia was found with an increase in the value of activated partial thromboplastin time (APTT) increasing to 67.1 (normal value 24 to 36). In further examination, the von Willebrand factor result was less than 2%. After the patient reaches 39 weeks of gestation it is decided to terminate the pregnancy. Pregnancy termination is performed by induction of 25 mcg misoprostol every 6 hours if preparation is optimal with intravenous desmopressin therapy and administration of cryoprecipitate transfusion if bleeding occurs. After surgery, a baby girl was born crying with active movements. Physical examination found no congenital abnormalities in the baby and the birth weight was 3540 grams, body length was 48 cm and the APGAR score was 7 in the first minute and 8 in the fifth minute.***

Keywords: pregnancy, von Willebrand's disease

1. Introduction

Von Willebrand's disease is one of the most common congenital bleeding disorders. Only a few of the world's population have this disorder and it is inherited autosomally. This condition is caused by a von Willebrand Factor (vWF) defect both quantitatively and qualitatively. This factor is an adhesive protein that binds platelets to the exposed subendothelium and carries factor VIII (FVIII) in the circulation.

Women experience naturally occurring physiological events such as menstruation, pregnancy and childbirth that put them at risk of excessive bleeding even if they do not have a bleeding disorder. Pregnancy is considered a hypercoagulable condition because several hemostatic factors increase during this time. This change is an adaptive change that prepares the body for hemostatic challenges at the time of delivery.1 Therefore, women with von Willebrand's disease who experience bleeding during pregnancy need to be thoroughly evaluated in order to determine the appropriate hematological and obstetric interventions for their conditions. each individual.

In this paper the authors review a case of pregnancy in the third trimester with a history of von Willebrand's disease where the patient does not routinely control medication and includes the latest theoretical studies in order to provide benefits in clinical practice at a later date. Von Willebrand's disease in pregnant women is a very rare case, especially at the Sanglah Denpasar-Bali Central General Hospital (RSUP), thus encouraging the author to discuss this case.

2. Method

This observational retrospective descriptive study was conducted at Sanglah General Hospital Bali from 1 January 2018 until 31 December 2019. The inclusion criteria were a pregnant woman with PROM who labored at Sanglah General Hospital during the study period and had complete maternal and neonatal medical records. The exclusion criteria were patients not willing to participate in this study.

PROM is defined as the rupture of amniotic membranes without sign of labor within one hour after the rupture of amniotic membranes. The characteristics included in this study were age, parity, PROM duration, PROM risk factors, type of labor (i.e. vaginal delivery, assisted vaginal delivery, and cesarean section), the indication of cesarean section, neonatal birth weight, maternal and perinatal morbidities, and types of neonatal care (i.e. regular ward or neonatal intensive care unit [NICU]). These data were analyzed as descriptive data using the Statistical Package for the Social Sciences (SPSS) for windows version 20.0 software.

3. Case Report

In this case report we present one case of pregnancy with a history of von Willebrand's disease. The patient with the initials KAE, aged 25 years, came for a referral from Ari Canti Gianyar Hospital with a diagnosis of her first pregnancy at 29 weeks' gestation with von Willebrand's suspected comorbidities. When the patient arrived, there were no complaints of abdominal pain, and there were no complaints of vaginal discharge, fetal movement was said to be still good, felt since March 2020, the patient complained of bleeding in the gums, no history of bruising or nosebleeds The patient had a history of von Willebrand's disease since the age of 17 but was not seen frequently.

Based on menstrual history, the patient was known to have menarche at the age of 14 years with a menstrual cycle of 28 days, regular, with a length of each menstruation for 7 days, with a volume of approximately 50 mL, and no complaints of pain during menstruation. The patient is currently pregnant with the first day of her last menstrual period on October 8, 2019 and the presentation of delivery on July 15, 2020. The patient underwent ANC examinations more than 3 times in obstetric gynecology specialists and midwives. The patient does not have a specific medication history, history of surgery, a history of certain allergies or a history of previous blood transfusions. Based on previous medical history, the patient was diagnosed with von Willebrand's disease at the age of 17 and her younger brother was also diagnosed with the disease.

On physical examination, he found a good general condition with compos mentis awareness. Vital signs are within normal limits and physical examination is within normal limits. On examination of the obstetric status, the uterine fundal height was found at 26 cm in the absence of his and the fetal heart rate was obtained 136 beats per minute. On laboratory examination, a mild microcytic hypochromic anemia was found with an increase in the value of activated partial thromboplastin time (APTT) increasing to 67.1 (normal value 24 to 36). In further examination, the von Willebrand factor result was less than 2%. After the patient reaches 39 weeks of gestation it is decided to terminate the pregnancy. On ultrasound examination, the estimated fetal weight is 3550 grams. Pregnancy termination is performed by induction of 25 mcg misoprostol every 6 hours if preparation is optimal with intravenous desmopressin therapy and administration of cryoprecipitate transfusion if bleeding occurs. Patients also received ferrous sulfas therapy every 12 hours, vitamin C every 12 hours, and an intravenous injection of octanate 1000 units 2 hours before delivery. Subsequent termination of pregnancy is performed by caesarean section.

After surgery, a baby girl was born crying with active movements. On the examination of vital signs, the fetal heart rate was found to be 148 beats per minute with regular breaths of 40 times per minute and body temperature of 36.9oC and oxygen saturation of 96%. Physical examination found no congenital abnormalities in the baby and the birth weight was 3540 grams and body length was 48 cm. In infants, the head circumference was 34 cm, chest circumference 34 cm and the APGAR score was 7 in the first minute and 8 in the fifth minute. The baby is then given an injection of Hep B and vitamin K and the newborn is treated with breast milk on demand.

Figure 1: A baby born to a girl weighing 3540 grams, body length 48 cm, and an APGAR score of 7-8. From physical examination found no congenital abnormalities.

4. Discussion

Von Willebrand's disease is the most common bleeding disorder inherited in women with a prevalence of 0.6 - 1.3% .2 This condition is a hereditary blood clotting disorder. Even though platelets are present in normal numbers, they cannot function properly due to the absence of von Willebrand factor (vWF) which is responsible for linking collagen to Glycoprotein Ib (GpIb) and Glycoprotein IIIa (GpIIIa) and accompanied by decreased levels of Factor VIIIC (FVIIIC).3

Von Willebrand disease is characterized by a deficiency of vWF and a decrease in the endogenous secretion of FVIII in the circulation. This reduction in FVIII secretion occurs secondary to reduction of vWF and the level and function of FVIII in plasma is related to vWF levels. The FVIII / vWF ratio of complexes in plasma is normally 1:50. This ratio allows an adequate vWF supply to bind to FVIII and form the vWF: FVIII complex.

The diagnosis of von Willebrand's disease can be made clinically and from biological information.4 An individual with a history of bleeding will show a primary hemostatic disorder, especially if supported by a family history.5

Clinical manifestations are generally indicated by mucocutaneous and soft tissue bleeding.1,5 The severity of this bleeding varies depending on the degree of reduction in vWF and FVIII as well as other factors. This bleeding tendency was generally heavier in type 3 and the lightest in type 1.1

Abnormal uterine bleeding is the most common symptom reported by women with von Willebrand's disease and approximately 74 - 92% experience excessive menstrual bleeding. Additional symptoms that may be encountered are epistaxis (38 - 63%), bleeding gums (26 - 35%), bleeding after tooth extraction (29 - 52%), bleeding due to minor trauma or abrasion (36%), postoperative bleeding (20 -28%), gastrointestinal bleeding (14%), joint bleeding (6 - 8%). [2]

The first stage in the evaluation of a woman with a suspected bleeding disorder is to obtain detailed information about the medical history and perform a physical examination. Women with excessive menstrual bleeding since menarche, postpartum or postoperative bleeding coupled with other bleeding symptoms such as bruising, epistaxis, bleeding gums, or having a family member with a history of bleeding should be considered to have von Willebrand's disease.4 In this case the patient was a woman aged 24 years who has been diagnosed with von Willebrand's disease since the age of 17 and has a positive family history where one of the patient's younger brothers has died from von Willebrand's disease. Bleeding gums that the patient complained about were a clinical manifestation of this hemostatic disorder.

Physical examination findings that point to bleeding disorders include, for example, ptechiae, ecchymosis, or a previous history of overt bleeding. The absence of signs of bleeding cannot exclude the possibility of a bleeding disorder.2

Patients with a positive screening history should undergo laboratory testing. Bleeding time prolongation is the result of classical laboratory tests to determine the presence of primary hemostasis disorders, but it should be remembered that the bleeding time examination is not specific and insensitive.5 Ideal laboratory tests for the exclusion of bleeding disorders are still not available but special tests such as von Willebrand Ristocetin Co Factor (RiCoF), vWF antigen (vWF: Ag), and factor VIII can be done.

Based on laboratory examination, this patient had a normal platelet count but the aPTT was slightly prolonged. Low FVIII and vWF confirmed the suspicion of a diagnosis of von Willebrand's disease at the time of examination. While platelet aggregation (Ristocetin Induced Trombosit Agglutination / RIPA) and normal ristocetin rheology results indicate that the patient has the mildest manifestations and the most common is von Willebrand disease type I.

At the time of pregnancy some hemostatic increases such as factor VII, factor X, fibrinogen and plasminogen activator inhibitor type 1 thus creating a hypercoagulable state. These changes are adaptive to prepare for labor. von Willebrand factor and FVIII also increase significantly during pregnancy with levels highest during the third trimester and levels exceeding 100 U / dL at delivery.

However, during delivery, several obstetric complications can cause bleeding. Post Partum Hemorrhage (PPH) is a major cause of complications and maternal mortality, especially in low-income countries. Therefore, the use of uterotonics immediately after delivery is recommended for all women to reduce this risk.1 Post Partum Hemorrhage itself is defined as blood loss> 500 mL at the time of vaginal delivery and> 1000 mL at the time of cesarean section.[6]

In this patient, only spontaneous bleeding in the form of bleeding gums was experienced when the patient brushed his teeth. This complaint only occurs a few times and always stops on its own without requiring medical treatment. While being treated at the hospital, the patient experienced epistaxis and immediately stopped after inserting a tampon. At the time of delivery, termination of pregnancy with SC Cito, as well as in post partum care there was no acute bleeding and the patient was allowed to go home.

Special attention needs to be paid to women with von Willebrand's disease who are pregnant because they are at risk of spontaneous abortion and post partum hemorrhage. It remains unclear whether women with von Willebrand's disease have an increased risk of spontaneous abortion. However, determining the mode of delivery, epidural management, and operative delivery techniques must also be done with a lot of consideration because women with von Willebrand's disease clearly have an increased risk of bleeding when compared to women without bleeding disorders.

Patients with bleeding disorders have a high risk of developing epidural or spinal hematoma. Many experts suggest that women with von Willebrand's disease should have a vaginal delivery because it is safer and a vaginal delivery can be performed as indicated. Keep in mind that von Willebrand's disease can be inherited in an autosomal dominant or recessive manner so that the fetus has a 50% risk of developing von Willebrand disease. Therefore, moderately invasive procedures such as the fetal scalp electrode or fetal scalp sampling should be avoided and circumcision should be postponed until the vWD status is known. Operative vaginal delivery, which can increase the risk of trauma to the infant, should also be avoided because of the risk of intracranial bleeding.

The condition of pregnancy affects the hemostasis in the body resulting in a procoagulant state, where under the influence of this pregnancy hormone, coagulation factors such as VII, VIII, X, and vWF increase. This is the body's compensation against the risk of bleeding during labor. Women with von Willebrand's disease also experience these hemostatic changes. This increase in vWF varies with the type of von Willebrand disease and does not appear to reduce the risk of bleeding compared with women without von Willebrand disease. The increase in VWF and FVIII occurred during the second trimester and peaked during the third trimester. VWF can progressively and reversibly acquire quantitative and qualitative changes during pregnancy.[7,8]

In this patient, in 2014 the vWF examination was 1%, the platelet aggregation was normal, and the rheology result of ristocetin was normal. For this pregnancy, the vWF level was re-examined at 35 weeks of gestation and a low vWF result was obtained, namely <2%.

The majority of women with vWD do not experience problems during their pregnancy but because they have a high risk of developing PPH if not treated, a multidisciplinary approach to management involving obstetricians, anesthetists and hematologists will provide optimal therapeutic results.2, 5 Collaboration with specialists hematology is also recommended if the patient is going to undergo surgery. This consultation with a hematologist

specialist allows discussion of vWF replacement, optimization of hematological parameters for epidural anesthesia and the use of vWF or factor VIII when needed to control bleeding.

The risk of bleeding is low when the ristocetin vWF co-factor assay is> 50 IU / dL. Below this level, therapy may be needed to prevent or control bleeding that occurs such as bleeding early in pregnancy or before invasive procedures. Measurement of vWF and FVIII levels at 34 weeks' gestation is considered adequate for most patients if there are no complications in pregnancy. If a level less than 50 IU / dL is found at week 34, corrective therapy for VWF and FVIII should be considered for delivery.

In this case, vWD management has been carried out according to the obstetric vWD management checklist in pregnancy, including: vWF examination at visit and 34 weeks of gestation, asking about bleeding history, handling with a multidisciplinary approach, hormonal and non-hormonal therapy of von Willebrand's disease, and preparation for SC surgery.

In the postpartum period, women with von Willebrand's disease need to be monitored for abnormal bleeding because factors VIII and vWF will fall to baseline levels immediately after delivery.[5, 9] Levels of vWF in the third trimester are inversely proportional to the risk of PPH, so monitoring is necessary for anticipation. However, in one study covering 2,238 samples it was found that only 32% of women had vWF monitoring in the third trimester. The incidence of PPH was 6.5%, of which 73% of cases occurred within one-week post-partum and 17% occurred on a delayed basis or more than two weeks post-partum. Excess menstrual bleeding was reported in 4.7% of women in the first three months after delivery. Forty-four samples required transfusion of packed red blood cells in the first three months post-partum, of which 93% required transfusion in the first 6 weeks.[10]

Patients in this study received Desmopressin for three days, cryoprecipitate and Octanate for 5 days. This is done to optimize hemostasis both before termination of pregnancy and discharge of the patient. The patient was discharged on the seventh day after cesarean section with the last complaint being epistaxis on the second postoperative day. This patient also did not receive long-term prophylaxis because based on the study of von Willebrand disease type 1, there were only minimal clinical manifestations. Education regarding the possibility of delayed bleeding after childbirth has been given so that if the patient experiences complaints of bleeding in the future, he can immediately seek medical help.

The patient experienced normal bleeding in the form of lochia from day-1 to day-7 post-SC treatment. On day 2, the patient had twice as much re-epistaxis which was finally controlled. There is no significant bleeding.

5. Conclusion

In this case report, the patient is a 24 year old woman with a third trimester of pregnancy who is accompanied by complaints of bleeding. The patient was diagnosed with suspected von Willebrand disease based on the clinical manifestations of frequent bleeding from the gums and a family history of disease in which the patient's two younger brothers had coagulation disorders. Screening was performed in these patients with prolonged aPTT results but normal platelet aggregation and ristocetin. This can happen because the patient is pregnant. Previously, the patient had been diagnosed with von Willebrand's disease at the age of 17 with complaints of bleeding gums but had never undergone routine monitoring. Team collaboration was carried out to determine the management of therapy and termination in these patients. The patient undergoes cesarean section when the gestational age approaches 40 weeks. During the operation, the patient experienced bleeding as much as 950 ml with PRC and cryoprecipitate preparations. After cesarean section, the patient bleeds for at least 7 days. At the time of treatment after cesarean section on the second day the patient experienced epistasis 2x but it was resolved. There is no significant bleeding. During hospitalization, patients received desmopressin, octanoate, and tranexamic acid therapy in accordance with existing theoretical studies.

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