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VON WILLEBRAND DISEASE IN PREGNANCY

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Abstract : Von Willebrand disease is the most common inherited bleeding disorder, found in approximately 1 of the general population ,without ethnic differences(1,2).VWD is the result of a deficiency or defect in Von Willebrand factor ,the large multimeric protein which mediates platelet adhesion and serves as a carrier protein for factor VIII. There are three major types. Type 1 is the result of a partial ,quantitative deficiency of a structurally normal VWF, and accounts for 70-80 of all VWD patients. Type 2 includes several qualitative defects in VWF that affects its multimeric structure or function. Patients with type3 VWD are homozygous or doubly heterozygous for two mutant VWF alleles ,with a resulting complete deficiency of VWF and a secondary severe deficiency of FVIII. Although the autosomal inheritance pattern predicts that both sexes should be equally affected, there is a higher frequency of symptomatic VWD in women because of the haemostatic challenges of menses, pregnancy and delivery(3-5). Pregnancy in these women requires specialised and individualised management provided by a multidisciplinary team of obstetricians, haematologists and anaesthetists.

Keyword :VWD, Factor VIII,VWF

INTRODUCTION :

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, found in approximately 1% of the general population ,without ethnic differences(1,2).VWD is the result of a deficiency or defect in Von Willebrand factor ,the large multimeric protein which mediates platelet adhesion and serves as a carrier protein for factor VIII(FVIII). There are three major types. Type 1 is the result of a partial ,quantitative deficiency of a structurally normal VWF, and accounts for 70-80% of all VWD patients. Type 2 (20% of VWD patients) includes several qualitative defects in VWF that affects its multimeric structure or function. Patients with type3 VWD (5-10% of VWD patients) are homozygous or doubly heterozygous for two mutant VWF alleles ,with a resulting complete deficiency of VWF and a secondary severe deficiency of FVIII. Although the autosomal inheritance pattern predicts that both sexes should be equally affected, there is a higher frequency of symptomatic VWD in women Because of the haemostatic challenges of menses, pregnancy and delivery(3-5). Pregnancy in these women requires specialised and individualised management provided by a multidisciplinary team of obstetricians, haematologists and anaesthetists. Advance planning in addition to good understanding and awareness of the potential maternal and neonatal complications are essential in ensuring an optimal outcome.

CASE REPORT: A 26 year old Primigravida had her booking visit in CMC at 10weeks of gestation ,following a referral for a hematoma she had developed after an intramuscular injection. Her childhood was uneventful. Her elder sister died of postpartum hemorrhage. There is history of bleeding symptoms in her sister's daughter for which she was evaluated and was diagnosed to have von Willebrand disease (VWD) type 2B. The patient was referred to haematology where she was evaluated. Tests done showed normal platelet count, bleeding time, prothrombin time and activated partial thromboplastin time within normal levels of factors VIII,IX,XI and fibrinogen. Low levels of Von Willebrand antigen and a low VonWillebrand factor to ristocetin ratio were detected. There was an increased platelet aggregation with low levels of ristocetin. Based on these reports a diagnosis of Von Willebrand disease type 2B was made. Subsequent antenatal visits showed an appropriately grown fetus and the patient remained asymptomatic. Her platelet count fell to 16,000 at 32weeks gestation and then to 12,000 at 36weeks gestation, but as she was asymptomatic, the haematologists did not advise any intervention. An ultrasound done at 38weeks showed the fetus to be in breech presentation. She was planned for external cephalic version with platelet transfusion cover. She spontaneously ruptured membranes and underwent an emergency caesarean section under cover of platelet transfusion and delivered a term ,girl baby weighing 2500g,which cried at birth. She received platelets post-operatively as her platelet count remained low and she had an ooze from the surgical site. She eventually required a haemostatic suture to control the bleeding from the subcutaneous tissue. She was discharged on the 6th post-op day and she was well at that time.

Discussion:

Von Willebrand disease is the most common inherited bleeding disorder with a prevalence of 1%. It is the result of quantitative or qualitative defect in VWF, a large multimetric protein that mediates platelet adhesion as a carrier protein for factor VIII. Three main types of VWD exist. Type I VWD is characterised by a partial deficiency of VWF. It accounts for 70-80% and is mild. Type 2 VWD is caused by functional defect of VWF protein. It consists of four subtypes based on their different pathophysiology. Types 1 and 2 transmitted as autosomal dominant trait. Type3 VWD is virtual absence of VWF, is severe and has an autosomal recessive inheritance

Physiology in pregnancy.

There is a progressive increase in FVIII and VWF levels during normal pregnancy .Most studies suggest an increase beginning during the second trimester, with peak levels at term, followed by a return to baseline during the postpartum period(6-12). FVIII and VWF levels also increase in most women with VWD, which may explain the frequent improvement in minor bleeding manifestations during pregnancy. The haemostatic response to pregnancy depends on both the type and severity of disease. Most women with type 1VWD have a progressive increase in FVIII and VWF levels into the normal non-pregnant range, which may mask the diagnosis during pregnancy .However, levels may remain low in severe cases. FVIII and VWF antigen levels often increase during pregnancy in women with type 2 VWD. Most studies show minimal or no increase in VWF activity levels, and a persistently abnormal pattern of multimers, reflecting the increased production of an abnormal VWF. Most women with type 3 VWD have no improvement in FVIII or VWF levels during pregnancy, although an increased FVIII level has been rarely reported. Very few studies have measured FVIII and VWF levels during the postpartum period. The limited available evidence suggests marked inter-individual variability in the rate of decline of FVIII and VWF levels after deliver. However, VWF levels may fall precipitously after delivery in women with VWD. The changes in clotting factor levels during and after pregnancy are assumed to parallel fluctuations in hormone levels, although there are no studies showing a direct correlation. Due to these variations in Factor VIII and VWF antigen levels during pregnancy, it is important to check their levels in the 3rd trimester, especially close to term to make sure that the levels are > 50 IU/dl. Values above this usually do not bleed excessively during procedures and at delivery.

CLASSIFICATION OF VON WILLEBRAND DISEASE :

Category	subtype	Defect	
TYPE 1		Quantitative	Partial quantitative deficiency of VWF.
ITYPE 2	2A	Qualitative	Decreased VWF – dependent platelet adhesion with deficiency of high – molecular –weight VWFmultimers.
	2B		Increased affinity for platelet binding protein GPIB
	2M		Decreased VWF – dependent platelet adhesion without deficiency of high- molecular- weight VWFmultimers.
	2N		Impaired binding of factor VIII
Type 3		Quantitative	Virtual absence of VWF.

VWF -Von Willebrand factor.

Diagnosis.

Basic haemostasis evaluation include complete blood count, platelet count, activated partial thromboplastin time (aPTT), protrombin time and fibrinogen levels. The intial work up is mainly to rule out other potential causes of bleeding. The aPTT is often normal in VWD, and only the most severe deficiencies with very low levels **of** FVIII will have a prolonged aPTT (13). If on initial evaluation the aPTT is prolonged ,it should correct on a 1:1 mixing with normal plasma to be consistent with VWF. If the initial test results return normal or show a prolonged aPTT that corrects with mixing, further testing is indicated. The following 3tests should follow. The first test is the VWF protein (VWF:Ag) assay which measures the VWF protein in plasma. The second test to be performed is a functional assay (VWF:RCo) that measures the interaction between VWF and platelets. The binding between these 2 and subsequent formation of platelet clumps is stimulated by the addition of antibiotic ristocetin.The third test,the FVIII assay measures the activity of FVIII which is a surrogate for the activity of VWF as a carrier protein for FVIII. The low-dose ristocetin –induced platelet aggregation test is valuable in diagnosing type 2B VWD. In this test ,low doses of the antibiotic ristocetin are added which will induce platelet aggregation .This test will be negative in all other subtypes of the disease. Ratio of VWF:RCo/VWF:Ag is performed to detect qualitative to quantitative dysfunction. This will differentiates type2 and type1 VWD variants.If the ratio is <0.5-0.7 the patient is most likely affected with type 2 disease's ,value <30IU/dL is diagnostic for VWD.

Complications during pregnancy and labour.

Women with VWD are not at an increased risk of miscarriage, however, they may manifest with excessive bleeding during a spontaneous or induced abortion. Women withVWD are at an increased risk of both primary and secondary postpartum haemorrhage (PPH). The risk of PPH is related to factor levels which decline after delivery. The rate of decline is variable and therefore the risk of bleeding persists up to 3-5 weeks after delivery(14). The key in avoiding PPH in this group is an increased awareness of this problem and use of preventive measures such as correction of coagulation defects and active management of third stage. In case of operative delivery meticulous haemostasis should be practised during surgery to minimise blood loss care must also be taken to minimise maternal genital and perineal trauma as these women are at particular risk of developing perineal haematoma. Management of PPH in these women presents a particular challenge to the clinicians and close collaborations between haematologists , obstetricians and anaesthetists are imperative. The use of neuraxial anesthesia in patients with VWD is generally not considered safe, other than for VWD type 1 with Factor VIII levels > 50IU/dl..In general prophylactic cover is recommended for women with VWF, F VIII or FIX levels less than 50 IU/ dl at term and they should be maintained above this level for atleast 3 days after vaginal delivery or 5 days after caesarean section as the pregnancy induced rise in clotting factors fall after delivery . The average time of presentation of PPH in women with VWD has been found to be15.7 +5.2 days It is recommended that cord blood sample is collected from neonates at risk of moderate or severe inherited bleeding disorders to assess coagulation status and clotting factor levels. This enables early identification and management of newborns at risk of haemorrhagic complications.

Management:

Most patients with Type1 disease tolerate pregnancy well. Type 2 disease has a variable prognosis. Treatment option includes desmopressin, antifbrinolytic agents, blood products and factor concentrates. Desmopressin is a synthetic analogue of vasopressin and acts by increasing Factor VIII and VWFlevels. It is only found to be useful in Type 1 VWD and may actually be detrimental in some forms of Type 2 disease. The preferred therapy for type-2 disease is the use of VWF concentrates(15). The concern about its use in pregnancy is mainly due to the worry of vasoconstriction (causing placental insufficiency), oxytocin effect(leading to preterm labour) and hyponatremia Tranexemic acid and other drugs of the similar class have been used as a djuncts during procedures and labour and delivery to control the bleeding. Platelet rich concentrates, cryoprecipitate and VWFFactor VIII concentrates are used when desmopressin fails/cannot be used in general, when the Factor VIII and VWF antigen levels are < 50 IU/dl and

the woman needs a procedure or when delivery is imminent.

Conclusion:

Optimal obstetric management of women with inherited bleeding disorders requires a good understanding of these disorders and an awareness of potential maternal and neonatal complications. A prospective of individualised management strategy should be formulated collaboratively by a multidisciplinary team of obstetricians, haematologists and anesthetists . It is generally suitable for women with a mild bleeding disorder to have a shared antenatal care between their local obstetric unit and tertiary centre with the delivery planned at their local unit. Women with severe disease should deliver at tertiary unit. The plan of management should be well documented in a case note with the copy given to the women to allow effective communication. Availability of management guidelines can help to minimise maternal and neonatal complications. These measures collectively will improve the care provided for these women and their pregnancy outcome.

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