Pregnancy and delivery of a women with Von Willebrand disease type 3: a case report

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INTRODUCTION

Von Willebrand disease (VWB) is the most common inherited bleeding disorder, found in approximately 1% of the general population, without ethnic differences. In 1926, Erik Von Willebrand first described a familial bleeding disorder in which symptoms were more severe in children and young women. He also noted that the condition had autosomal inheritance and that blood transfusions improved bleeding symptoms. Since then knowledge of this disease has grown exponentially and is currently recognized as the most common inherited bleeding disorder. VWB disease is the result of a deficiency or defect in Von Willebrand factor (VWF) the large multimeric proteins which mediate platelet adhesions 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 Type 3 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 hemostatic challenges of menses, pregnancy and delivery. There is a progressive increase in FVIII and VWF levels during normal pregnancy. The challenge of managing Von Willebrand disease is the availability of Factor VIII with vigilant care to be taken during antenatal, intra-partum and postnatal period.

CASE REPORT

This 2-year-old primigravida spontaneous conception a known case of VWD type 3 at 36 week + 4 days of period of gestation was transferred to our hospital for delivery with no previous antenatal checkup at our hospital with no genetic evaluation. On history patient had history of excessive blood loss during her periods and was put on continuous oral contraceptive pills since menarche. There was no bleeding from nose, gums
or bleeding in joints in childhood. During pregnancy
there no history of bleeding from nose and gums or that
of threatened abortion. Her brother had also been
suffering from similar disease.

On examination general condition of patient was good
and there was no pregnancy related complications. Her
Hb was 11 gm/dl. APPT- C-35 sec and T-48 sec, VWF-
01% and Factor VIII-04%. All the other antenatal
investigations and test for fetal well-being were within
normal limits. As this patient reported late in the
pregnancy and in the absence of maternal genetic
evaluation, prenatal diagnosis could not be offered to her
to prognosticate the fetus.

She remained asymptomatic and was managed
conservatively. There was no requirement of FVIII-VWF
concentrate nor any blood products during antenatal
period. However, in consultation with the hematologist
VWF was demanded, dose was calculated and there was
preparedness in the eventuality of any emergency. She
spontaneously went into labor at 40 weeks POG when
she was administered 2500 u units of VIII-VWF at the
onset of labor.

Table 1: Relation of VWF and VIII levels with post op day and action taken.

| Day of surgery | VIII level | VWF level | APPT | VIII-VWF transfused |
|---------------|------------|-----------|------|---------------------|
| 0             | 93%        | 62%       | C-35 sec, T- 37.3 sec | 2500 U |
| 1st           | 132%       | 43%       | C-32 sec, T-39 sec   | 1000 U |
| 2nd           | 160%       | 64%       | C-33 sec, T-37.4 sec |         |
| 3rd           | 125%       | 44%       | C-35 sec, T-48.2 sec |         |
| 4th           | 48%        | 15%       | C-35 sec, T-50.7 sec | 1000 U |

Her blood investigations revealed APTT- C- 35 sec and
T- 39 sec. Factor VIII levels were - 93%, VWF levels
were - 62%. She was taken up for caesarean section due
to Non progress of labour. Team of anesthesiologists
selected general anaesthesia with acid aspiration
prophylaxis for surgery. Cesarean was performed and
perfect hemostasis was ensured at each step with
cauterization of minor bleeding points. The bleeding after
placental separation was not excessive. Uterus was
repaired in two layers; Intraperitoneal drain was placed as
post op bleeding was anticipated. Patient was monitored
intensively in the post-op period. In the evening patient
started oozing from wound and drain site which was
controlled with compression bandage however this ooze
continued for 2 days where was requirement of
administration of Von Willebrands factor.

On 1st post op day- Hb-15 gm /dl, platelet-1.09 lakh and
total drain output was about - 1000 ml, bloody in nature.
No PPH or bleeding from any other site. On 2nd post-op
day - total drain = 250 ml sero-sanguineous in nature and
Drain removed. Stitches were removed on day 14 and
Patient was discharged to home. The association of the
levels of VWF and the requirement of factor infusion is
depicted in Table 1.

DISCUSSION

The hemostatic response to pregnancy depends on both
the type and severity of the disease. Most women with
type 3 VWD have no improvement in FVIII and VWF
levels during pregnancy, although an increased FVIII
levels has been rarely reported.12,13 VMF levels may fall
precipitously after delivery in women with VWD.14 The
postpartum fall in VMF explains the risk of post-partum
hemorrhage, even in women with type 1 disease. Since

FVIII and VMF levels do not increase significantly until
the second trimester, women with VMD remain at risk
from bleeding in early pregnancy.12 Keeping in mind the
high possibility of bleeding in the post-partum period,
patient was prophylactically given VWF at the onset of
labor and an extra dose post-delivery. Though the patient
was asymptomatic in the antenatal period she didn’t
require any VWF supplementation, but with the
anticipation of bleeding in the patient blood and blood
products was kept ready in the blood bank to meet any
emergency. Meticulous execution of surgery was carried
out without much blood loss so as to minimize the
possibility of any intra-partum bleeding and prophylactic
placement of intraabdominal drain. Management of
VWD during pregnancy should ideally include
obstetricians, hematologist and blood bank personnel.
During the course of pregnancy, one of many physiologic
changes is an increase in several components of the
clotting cascade; which includes both FVIII and VWF
levels. Consequently, many patients with VWD reach
normal levels of both FVIII and VWF at term. There
seems to be no consensus in the literature as to how often
levels of FVIII and VMF:RCo must be monitored.
However, there is an agreement that, at the very
minimum, levels should be determined during the third
trimester.11,15 Pregnant women with VMD are at higher
risk of hemorrhagic complications, mainly during the
post-partum period. Such events are far more common if
both FVIII and VMF:RCo levels are 50 IU/dl. Overall,
16-29% of women with VMD will have postpartum
hemorrhage within the first 24 hours of delivery, and 20-
29% women will experience delayed postpartum
bleeding. The third stage of labor should be managed
actively. Procedures that potentially could increase the
risk of hemorrhage (e.g. pudendal blocks, episiotomies,
fetal scalp electrodes or operative vaginal deliveries)
should be avoided if possible. The usual loading dose of these products is 40-60 IU/kg.\textsuperscript{16} VMF concentrates are dosed primarily on the basis of VMF:RCO units and secondarily on the basis of FVIII units. Infusions ideally should start before delivery until levels of 50IU/dl are achieved for both VMF:RCO and FVIII levels. Such levels should be maintained for at least 3-5 days after delivery. Levels should be followed daily, and the need for repeated doses should be tailored accordingly. Maintenance dose usually range between 20 and 40 IU/kg every 12-48 hours. As started before, because the risk of delayed post-partum hemorrhage, laboratory monitoring may be needed for 2 weeks after delivery to correctly identify those patients who will require prolonged prophylaxis with either VMF concentrate.

Genetic counseling and prenatal diagnosis

Genetic counseling about the risk of disease transmission and its variable expression should be provided to all women with VWD. This is particularly important for families with a child with type 3 VWD because each subsequent child has a 25\% chance of inheriting a similar severe disease. Prenatal diagnosis of VWD is performed by analysis of DNA extracted from fetal cell obtained by CVS at 10-12 weeks or amniocentesis at 16-18 weeks of gestation. In our case the prenatal diagnosis was not offered to the patient as she had presented late in the antenatal period. However, she is planned for genetic evaluation now to offer prenatal diagnosis in the next pregnancy.

CONCLUSION

The management of pregnancy with VWD entails involvement of a multidisciplinary team consisting of hematologist, critical care specialist, senior obstetricians and neonatologist with strict vigilance, thorough intraop haemoststis and administration of Von Willebrand’s factor especially in the intrapartum and post-partum period are critical and recommended for effective management of pregnancy with VWD 3.

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