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Management of von Willebrand disease type 3 during pregnancy – 2 cases reports

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Abstract. – BACKGROUND: Von Willebrand disease type 3, is an extremely rare condition. It can be severe and potentially life-threatening, particularly in pregnant women during labor and subsequently during early puerperium. Due to its rarity, there is no optimal treatment/management during pregnancy.

CASE: We describe two cases of pregnant women with von Willebrand disease type 3, and its successful surveillance and treatment with Haemate P FVIII (human plasma-derived von Willebrand Factor-ristocetin co-factor associated with human coagulation factor VIII), during pregnancy, partum and puerperium.

CONCLUSIONS: Daily prophylaxis with Haemate P FVIII in women with von Willebrand disease type 3, starting 2 hours before caesarean section until the 7th day of puerperium, associated with close analytical and clinical surveillance seems to be a safe clinical option.

Key words:
von Willebrand disease, Type 3, Pregnancy, Management

Abbreviations

VWD = von Willebrand disease; VWF = von Willebrand factor; FVIII = factor VIII; VWF:Ag = von Willebrand Factor antigen; VWF:RCo = von Willebrand Factor-ristocetin co-factor activity; FVIII:C = factor VIII activity; INR = International Normalized Ratio.

Introduction

Von Willebrand disease (VWD) is the most common inherited bleeding disorder. It results from a quantitative or qualitative deficiency of von Willebrand factor (VWF) – a large multimeric protein which is required for platelet adhesion and serves as a factor VIII (FVIII) carrier.

There are three major types:

– Type 1 (70-80% of all VWD patients) is the result of a quantitative defect of a structurally normal VWF.
– Type 2 (20% of VWD patients) includes several qualitative defects in VWF that affect its multimeric structure or function. Four subtypes exist: 2A, 2B, 2M and 2N.
– Type 3 (5-10% of VWD patients) are homozygous or doubly heterozygous for two mutant VWF alleles, which results in complete or almost complete absence of VWF and severe deficiency of FVIII.

The VWF gene is located on chromosome twelve. Types 1 and 2 are inherited as autosomal dominant traits and type 3 is inherited as autosomal recessive. Occasionally type 2 also inherits recessively. 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 menstrual period, pregnancy and delivery[1-3].

Despite the prevalence of VWD being very frequent, affecting 0.1% to 1% of the population[4-5], the prevalence of type 3 VWD, its most severe form, is extremely low, 3 to 5 cases per million people[6].

This bleeding disorder has a very diverse clinical presentation. It can vary from asymptomatic or mild symptoms in majority of patients (type 1 or 2), to a very severe clinical condition in a minority of patients (type 3), with recurrent bleeding episodes including hemarthroses, requiring replacement therapy.

The physiological response during pregnancy is the elevation of the factor FVIII and VWF (hypercoagulability state). However, in women with VWD type 3, this physiological increase in FVIII and VWF does not occur. Therefore, serious hemorrhagic complications, especially during labor and early postpartum, can be expected.

We describe the therapeutic orientation in pregnancy and post-partum, in two women, with VWD type 3.

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1st clinical case

32 years, primigravida, 63 kg in early pregnancy, with von Willebrand disease type 3 (VWF:Ag 0%, VWF:RCo 0%, FVIII:C 3%), diagnosed at age of 3 year-old. She had many bleeding episodes prior to pregnancy (worth noting: metrorrhagia, hemarthrosis, gastrointestinal angiodysplasia, haemoperitoneum) that led to several treatments with FVIII, VWF and red blood cell transfusions. During pregnancy, prevention of bleeding was performed with Haemate P 1.000 FVIII [2400 International Units (IU) human plasma-derived von Willebrand Factor-ristocetin co-factor activity (VWF:RCo) and 1000 IU human coagulation factor VIII activity (FVIII:C)] twice a week, during the first 12 weeks of gestation and restarting again at 34 weeks. Pregnancy was uneventful except for mild fetal growth restriction detected at 36 weeks. Labor was induced at 38 weeks of gestation (the pregnant woman was weighting 72 kg at this stage). A caesarean section was performed, because of labor induction failure (6h after the administration of Haemate P FVIII), which resulted in a female newborn, weighting 2370 g. The patient underwent prophylactic treatment, pre and post caesarean section, with Haemate P 1.500 FVIII (3600 IU human plasma-derived VWF:RCo and 1500 IU human FVIII:C) starting on the day of labor induction (2 hours before), followed by once a day, during 7 days. During labor, our anesthesiologists have chosen intravenous analgesia and general anaesthesia during caesarean section. The patient was discharged on the 7th day of puerperium, without complications.

2nd clinical case

29 years, primigravida, 61 kg in early pregnancy, with von Willebrand disease type 3 (VWF:Ag 0%, VWF:RCo 0%, FVIII:C 2%), diagnosed on the 3rd month of life . She had several bleeding episodes prior to pregnancy, namely epistaxis, hemarthrosis and moderate haemoperitoneum. Prophylaxis was made with Haemate P 1.000 FVIII (2400 IU human plasma-derived VWF:RCo and 1000 IU human FVIII:C) once or twice a week during the first 12 weeks of pregnancy and restarted again, twice a week, at 36 weeks of gestation. There were no complications during pregnancy, including blood loss. An elective caesarean was performed at 38 weeks of gestation because of breech fetal presentation. The newborn was male, weighting 2925 g. At the time of caesarean section the pregnant woman was weighting 75 kg. Like on the first case, the patient was submitted to prophylactic treatment with Haemate P 1.500 FVIII (3.600 IU human plasma-derived VWF:RCo and 1.500 IU human FVIII:C) starting 2 hours before caesarean section and once day during 7 days. As it was decided an elective caesarean, our anesthesiologists chose to perform a general anaesthesia in this case. The patient was discharged on the 7th day. The puerperium was uneventful.

Discussion

Pregnancy and childbirth, in women with VWD type 3, may be associated with severe bleeding, predominantly during labor and in postpartum. Mild vaginal bleeding in early pregnancy has also been described. In order to avoid this bleeding in early pregnancy, and because these two pregnant women were very anxious, it was decided to perform prophylactic Haemate P FVIII in the 1st trimester of pregnancy.

Although "if VWF:RCo and FVIII levels can be monitored and maintained above 50 IU/dL during labor and delivery, and no other coagulation defects are present, then regional anaesthesia may be considered"[7]; we avoided this type of analgesia/anaesthesia and opted for general anaesthesia.

Despite the risk of postpartum haemorrhage can persist for 2-3 weeks (15.7 ± 5.2 days after delivery)[8], many studies state that VWF:RCo and FVIII levels of 50 IU/dL should be achieved before delivery[9] and maintained for 3-5 days afterward[10-13]. However, caesarean section is considered a major surgery and guidelines advise to perform prophylaxis for a 7-14 days postoperative period[14,15].

In an attempted to give the minimum possible amount of factor, sufficient for prophylaxis (40-60 IU/kg body weight VWF:RCo and 20-40 IU/kg bodyweight FVIII:C)[14,15] and to prevent accumulation of dose (levels should not exceed VWF:RCo 200 IU/dL or FVIII 250-300 IU/dL)[14,15] which has been associated with some cases of venous thromboembolism, we opted to administer daily Haemate P 1.500 FVIII, starting 2 hours before labor induction or caesarean section (since peak plasma levels of VWF and FVIII usually occur at around 50 minutes and 1-1.5 hours, after injection, respectively), up to the 7th day of puerperium. As we gave low/prophylactic

dose of Haemate P FVIII, for a short period of time (until the 7th day of puerperium), we chose not to adopt antithrombotic prophylaxis with low molecular weight heparin but rather monitor closely these women in postpartum (the highest peak obtained was on the first case: VWF:Ag 120%, VWF:RCo 104% and FVIII:C 166%).

After hospital discharge, we have closely observed these women twice a week during the first 6 weeks of puerperium, looking for signs of bleeding. Puerperium was uneventful.

What is the best dose and treatment duration? How often and when is the best time that we should monitor analytically the values of VWF:Ag, VWF:RCo and FVIII:C? Due to the rarity of this disease, there is still no answer to these questions. We preferred to collect the analysis 2h after administration of Haemate P FVIII in an attempt to catch the peak plasma levels (to prevent overdosing) rather than collect the analysis prior to administration Haemate P FVIII since the VWF:RCo half-life is around 9,9h[16,17] and, therefore, we believe that after 24h the values will be subtherapeutic and/or approach null values (the average values of these patients without medication).

Conclusions

These two uncommon cases demonstrated that towards an uneventful caesarean section and puerperium in a woman with VWD type 3, prophylaxis in the peri-natal and during the first 7 postoperative days, associated with close clinical and analytical surveillance can be a safe clinical option, avoiding overtreatment side effects and/or longer hospitalizations.

Conflict of interest

The Authors declare that they have no conflict of interests.

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