

Research Letter

## Ovarian hyperstimulation syndrome associated with von Willebrand's disease

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Ascites and pleural effusion are common but are serious complications of ovarian hyperstimulation syndrome (OHSS). In critical cases of this syndrome, multiple paracenteses may be required to relieve the severe abdominal distention, hypotension, decreased renal perfusion, and severe respiratory compromise that can arise [1]. Continuous abdominal and pleural drainages are indicated in cases of massive ascites and pleural effusion [2]. However, the complications associated solely with the performance of paracentesis are infrequently reported. Furthermore, a clinical dilemma arises when patients with von Willebrand's disease (vWD) develop OHSS such that repeated abdominal paracentesis is required. vWD is the most common congenital hemorrhagic diathesis inherited as an autosomal dominant trait; the prevalence of this disease is estimated to be 1–2% of the population [3]. Mucocutaneous and surgical hemorrhage in affected individuals is caused by quantitative or qualitative defects in von Willebrand factor (vWF). This large multimeric protein supports platelet adhesion and aggregation during initiation of hemostasis at the time of vascular injury and functions as a carrier protein for circulating factor VIII [4].

In the present report, a patient with Type II b vWD and severe OHSS complicated by multiple skin ecchymosis and subcutaneous hematomas after performance of multiple paracenteses is described. Conservative treatment with parenteral administration of albumin and Haemate-P combined with a platelet transfusion served to prevent the serious sequelae of coagulopathy.

A 31-year-old infertile nulligravida woman with history of Type IIb vWD requested assisted intrauterine sperm insemination. Her infertility was attributable to a lack of ovarian

factor because of the presence of polycystic ovary syndrome (PCOS). Pituitary downregulation with busserelin acetate (Suprefact; Hoechst, Germany; 0.5 mg/d) was initiated on Days 2, 3, and 4 of her menstrual cycle followed by ovarian stimulation with a daily dose of 225 IU of subcutaneous Gonal-F for 6 days. At 12 days following initiation of ovarian stimulation, the patient developed eight dominant follicles ranging between 18 mm and 21 mm in diameter, and a peak serum estradiol concentration of 2,626 pg/mL was observed on the day of injection of 5,000 IU of human chorionic gonadotropin (hCG; Profasi; Serono Laboratories, Norwell, MA, USA). A standard intrauterine insemination was performed 36 hours later. Luteal phase support was provided by administration of Utrogestan (100 mg, three times daily, by vaginal suppository) with another intramuscular injection of 2,000 IU of hCG given on the 22<sup>nd</sup> cycle day.

The patient complained of acute abdominal distension, nausea, and vomiting; and 3.5 kg body weight gain were observed on the 25<sup>th</sup> cycle day. Severe OHSS was diagnosed on the basis of enlarged ovaries as observed by ultrasound and on the bases of massive ascites and pleural effusion as observed by plain chest film. Hemoconcentration and hypoalbuminemia were diagnosed by increased hematocrit (48.5%) and hemoglobin (18.5 g/dL) values in addition to a decreased albumin value (3.1 g/dL; normal reference, 3.5–5.3 g/dL). The prothrombin time (12.0 seconds) and the activated partial thromboplastin time (24.5 seconds) were both within normal limits.

The patient was treated with a large volume of plasma expander, and 100 g of human serum albumin was administered daily. Four attempts at abdominal paracentesis were performed to relieve dyspnea and abdominal distension, with up to 1,840 mL; 2,300 mL; 1,400 mL; and 1,100 mL of ascitic fluid drained between the 2<sup>nd</sup> and 6<sup>th</sup> hospital day. Thoracentesis was withheld because of thrombocytopenia, with platelet counts as low as 25,000/mm<sup>3</sup> obtained on the 4<sup>th</sup>

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hospital day. A platelet transfusion was initiated. Laboratory values were: hemoglobin, 13 g/dL; prothrombin time, 12.3 seconds (control, 13.0 seconds); activated partial thromboplastin time, 26.7 seconds (control, 36 seconds); bleeding time, 8.0 minutes (normal reference,  $2 \pm 7.5$  minutes). All vWF factor measurements were within the reference range of 132% (normal reference range:  $60 \pm 150\%$ ). On hospital Day 7, symptoms of OHSS improved; however, she developed multiple ecchymoses over her tapping sites. These ecchymoses coalesced into subcutaneous hematomas measuring  $40 \times 50 \text{ cm}^2$  in size. Following intravenous administration of 50 IU/kg of Haemate-P (factor VIII concentrate), hemostasis was restored. Her bleeding time returned to the normal range, which remained for the rest of her hospital stay. She was discharged on the 16<sup>th</sup> hospital day.

After a successful intrauterine insemination, a twin pregnancy was confirmed at gestational Week 6. However, a miscarriage of one embryo occurred at the 7<sup>th</sup> gestational week. The remaining male singleton was delivered uneventfully by the vaginal route at the 40<sup>th</sup> gestational week. Haemate-P replacement therapy was administered during the first stage of labor and was given continuously in combination with uterotonics for 3 days after delivery to avoid a bleeding episode. Following these treatments, a normal coagulation profile was achieved. Neither an immediate vaginal hematoma nor a late postpartum hemorrhage occurred following delivery.

Cases of acquired vWD of the Type IIb variety combined with OHSS have been reported only rarely. Type IIb vWD is attributable to a qualitative abnormality in the region of vWF responsible for the rapid clearance of its multimeric forms. These abnormal multimeric forms bind tightly to platelets, which are then rapidly cleared such that thrombocytopenia may occur. Most cases are associated with mucosal bleeding and present with epistaxis, gingival bleeding, or menorrhagia. The patient described in the present report denied having any incisional bleeding after surgery or dental extractions before admission. Laboratory findings for patients with Type IIb vWD include a normal platelet count and morphology, although bleeding time for these patients is usually prolonged. Because of the subclinical presentation of our patient, her bleeding time was not determined before induction of ovulation.

The clinical management of pregnancy and delivery for patients with Type IIb vWD is well described in the literature, and only one case of acquired hemophilia in the presence of OHSS has been reported [5]. Hemophilia was diagnosed on the basis of a reduction in factor VIII:C; all measurements related to vWF (factor VIII antigen, ristocetin cofactor activity) were normal. In the present case, the possibility of acquired hemophilia was excluded because factor VIII:C concentrations were within the normal range. Our patient also had normal vWF concentrations, consistent with the presence of the IIb subtype, which is associated with changes in the quality, as opposed to the quantity, of vWF.

Our patient exhibited bleeding times of up to 8 minutes in the absence of aspirin therapy. The reports of cases of thrombophilia caused by OHSS [6] contrast markedly with the present report in which severe thrombocytopenia (platelet

count of  $2.5 \times 10^4/\text{mm}^3$ ) was observed. That the thrombocytopenia was attributable to an increased binding of large multimeric forms of vWF to platelets such that the complexes were more rapidly consumed could not be established. Further studies are required to understand more fully the pathophysiology underpinning the relationship between OHSS and vWD.

In cases of PCOS, prolonged treatments with high doses of FSH may serve to induce OHSS. Based on the body weight (65 kg) of our patient, a daily dose of 225 IU FSH was required for the initial induction of ovulation; this treatment may therefore have been responsible for the development of her OHSS. It is also important to note that hCG should be withheld from PCOS patients during the luteal phase to avoid provoking severe OHSS. Furthermore, luteal phase administration of hCG is associated with a higher incidence of severe OHSS as compared with supplementation with progesterone alone [7]. Patients with PCOS should be informed of the high risk of OHSS before induction of ovulation.

The standard therapy for patients with vWD is a transfusion of plasma cryoprecipitate. Each unit of cryoprecipitate will raise vWF values approximately by 3%, and 10–15 units of cryoprecipitate may elevate vWF values by as much as 30–50%. Factor VIII antigen concentrations decline with a half-life of 12–18 hours, but the duration of the corrected bleeding time is usually shorter. New factor VIII concentrates, such as Haemate-P, that are now broadly available are anticipated to replace cryoprecipitate as the treatment of choice for patients with vWD [8,9]. Recommended dosages of these concentrates are 20–50 units/kg, depending on disease severity. In the case of our patient, Haemate-P was administered at later times than that are traditionally chosen. To correct her coagulopathy, a dose of 50 units/kg of Haemate-P was given on an emergency basis with a good treatment response. In patients with vWD, a significantly increased risk for hemorrhage exists during labor and delivery, particularly during the puerperium. However, vaginal delivery is reported to be generally free of such risk in patients with vWD [10,11]. The incidence of postpartum hemorrhage for these patients is 30%. The danger of postpartum bleeding complications cannot be predicted with certainty, either by past history of bleeding episodes or by laboratory tests designed to measure vWF activity [12]. Because of our previous success with Haemate-P in managing iatrogenically induced hematomas because of multiple abdominal paracenteses, Haemate-P was chosen for the present case to control bleeding during episiotomy.

In conclusion, patients with severe OHSS superimposed on vWD and for whom abdominal paracentesis is needed to relieve massive ascites are at risk for development of diffuse skin ecchymosis because of an underlying bleeding tendency. In patients with vWD, measurements of serum prothrombin time and activated partial thromboplastin time before induction of ovulation do not adequately evaluate bleeding tendency. Detailed coagulation profiles should be obtained for infertile patients with vWD before they undergo assisted reproductive procedures. Multiple abdominal paracenteses should be withheld from these patients if the possibility of subcutaneous hematoma persists.

## References

- [1] Levin I, Almog B, Avni A, Baram A, Lessing JB, Gamzu R. Effect of paracentesis of ascitic fluids on urinary output and blood indices in patients with severe ovarian hyperstimulation syndrome. *Fertil Steril* 2002;77:986–8.
- [2] Abuzeid MI, Nassar Z, Massaad Z, Weiss M, Ashraf M, Fakhri M. Pigtail catheter for the treatment of ascites associated with ovarian hyperstimulation syndrome. *Hum Reprod* 2003;18:370–3.
- [3] Cox Gill J. Diagnosis and treatment of von Willebrand disease. *Hematol Oncol Clin North Am* 2004;18:1277–99.
- [4] Budde U, Schnepfenheim R. Von Willebrand factor and von Willebrand disease. *Rev Clin Exp Hematol* 2001;5:335–68.
- [5] Nakauchi-Tanaka T, Sohda S, Someya K, Kono K, Hamada H, Yoshikawa H. Acquired haemophilia due to factor VIII inhibitors in ovarian hyperstimulation syndrome: case report. *Hum Reprod* 2003;18:506–8.
- [6] Ou YC, Kao YL, Lai SL, Kung FT, Huang FJ, Chang SY, et al. Thromboembolism after ovarian stimulation: successful management of a woman with superior sagittal sinus thrombosis after IVF and embryo transfer: case report. *Hum Reprod* 2003;18:2375–81.
- [7] McClure N, Leya J, Radwanska E, Rawlins R, Haning Jr RV. Luteal phase support and severe ovarian hyperstimulation syndrome. *Hum Reprod* 1992;7:758–64.
- [8] Lubetsky A, Schulman S, Varon D, Martinowitz U, Kenet G, Gitel S, et al. Safety and efficacy of continuous infusion of a combined factor VIII-von Willebrand factor (vWF) concentrate (Haemate-P) in patients with von Willebrand disease. *Thromb Haemost* 1999;81:229–33.
- [9] Franchini M, Rossetti G, Tagliaferri A, Pattacini C, Pozzoli D, Lippi G, et al. Efficacy and safety of factor VIII/von Willebrand's factor concentrate (Haemate-P) in preventing bleeding during surgery or invasive procedures in patients with von Willebrand disease. *Haematologica* 2003;88:1279–83.
- [10] Ito M, Yoshimura K, Toyoda N, Wada H. Pregnancy and delivery in patients with von Willebrand's disease. *J Obstet Gynaecol Res* 1997;23:37–43.
- [11] Guth U, Tsakiris DA, Reber A, Holzgreve W, Hosli I. Management of patients with Type 2B von Willebrand's disease during delivery and puerperium. *Z Geburtshilfe Neonatol* 2002;206:151–5 [in German].
- [12] Federici AB. Clinical diagnosis of von Willebrand disease. *Haemophilia* 2004;10:169–76.