Conservative management of massive hematoperitoneum caused by ovulation in a patient with severe form of von Willebrand disease - a case report

M. Terzic[1,2], I. Likic[2], I. Pilic[2], J. Bila[2], N. Knezevic[3]

[1]Department of Gynaecology and Obstetrics, University of Belgrade, Faculty of Medicine, Belgrade
[2]Clinic of Gynaecology and Obstetrics, Clinical Center of Serbia, Belgrade (Serbia)
[3]Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, IL (USA)

Summary

Von Willebrand disease (VWD) is the most common inherited bleeding condition that involves extended or excessive bleeding, caused by the deficiency or defect of von Willebrand factor (VWF). Hematoperitoneum as a complication of gynecologic diseases represents acute condition which is usually caused by the hemorrhagic corpus luteum or a rupture of either ectopic pregnancy or a hemorrhagic ovarian cyst. The authors present a unique case of conservatively managed massive hematoperitoneum caused by ovulation in a patient with severe form of von Willebrand disease who had right adnexectomy due to hemorrhagic corpus luteum four months prior. This conservative management by blood product and factor concentrate support could be a method of choice in selected hemodynamically stable patients. Furthermore, recurrent bleeding episodes following ovulation could be prevented by suppression of ovulation using oral contraceptive pills.

Key words: Hematoperitoneum; Ovulation; Von Willebrand disease; Conservative management.

Introduction

Von Willebrand disease (VWD) is the most common inherited bleeding disorder caused by a deficiency or defect of von Willebrand factor (VWF) [1, 2]. Type 3 of VWD is a very rare form of disease, characterized with a complete deficiency of VWF and secondary severe deficiency of F VIII [2]. Symptoms of VWD are more common in women considering that they are exposed to hemostatic risks during the menstrual period or pregnancy / delivery during their reproductive period [2, 3].

Hematoperitoneum as a complication of gynecologic diseases represents an acute condition which requires operative treatment. It is usually caused by a hemorrhagic corpus luteum or a rupture of either ectopic pregnancy or hemorrhagic ovarian cyst [4]. Hematoperitoneum secondary to ovulation is rare, and in most cases is associated with severe bleeding disorders, such as afibrinogenaemia or VWD's, or in patients undergoing anticoagulation therapy [5, 6].

The authors present a unique case of conservatively treated hematoperitoneum caused by ovulation in a patient with severe (type 3) form of VWD.

Case Report

A 38-year-old woman was admitted to the hospital due to a deteriorated general condition, followed by tenderness in the lower part of the abdomen. The patient suffered from a severe form of VWD since childhood. The patient had two normal vaginal deliveries with life-threatening postpartal hemorrhages, but without any additional data regarding their management. All menstrual periods were hypermenorrhoic. The patient had adnexectomy on the right side due to adnexal tumor formation four months prior. The tumor was histopathologically verified as a hemorrhagic cyst with hydrosalpinx. Both surgery and postoperative period were uneventful, while the patient was on VWF / FVIII complex therapy (Haemate P 2000 IU i.v.).

The patient was pale, generally weak, but with stable blood pressure. During the gynecological examination, an adnexal mass about five cm in size was verified on the left side. The adnexal mass was mobile, elastic, smooth-surfaced, and palpatory tender, but without peritoneal irritation. The laboratory results showed a low hemoglobin level (Hgb - 88 g / L), while parameters for infection (WBC, CRP), and β-HCG were negative. The level of CA-125 was slightly elevated (42.2 IU / L), and other tumor markers (AFP, CA 19.9, CA 15.3, CEA) were within normal range. Value of VWF at that moment was zero percent, and other parameters of hemostasis were as follows: PT 13.2 s, a PTT 28.7 s, INR 1.21, fibrinogen 3.4 g / L, AT 60.5%, D-dimer 2.31 mcg / L. Transvaginal ultrasound (TVUS) examination verified a hypoechoic mass (40 x 30 mm) in the left adnexal region, clearly marked with blood clot on its surface and surrounded with suspected hemorrhagic cyst rupture or state after ovulation. There was a moderate amount of free fluid in Douglas's pouch with several small blood clots sized up to two cm (Figures 1A and B).

The patient was transferred to the intensive care unit, and therapy with 20 IU of cryoprecipitate was begun. In order to assess the patient's condition and further therapeutic possibilities, magnetic resonance imaging (MRI) of abdomen and pelvis were performed. An MRI of the abdomen showed enlarged spleen (15 cm in cranio-caudal diameter), as well as a right lobe of the liver. In projection of the left adnexa, there was an oval, clearly marked formation, 4.7 x 4 cm in diameter. There were several follicles on the left ovary. Posterior to this formation and behind the uterus, there was an organized clot formation with

Revised manuscript accepted for publication March 20, 2012

Fig. 1A

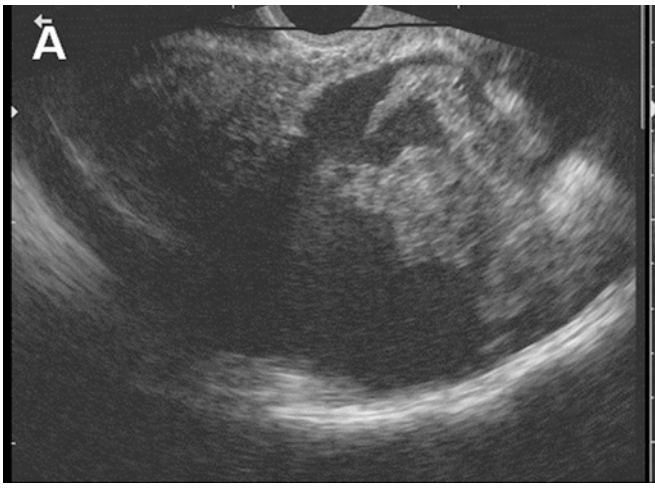

Fig. 1B

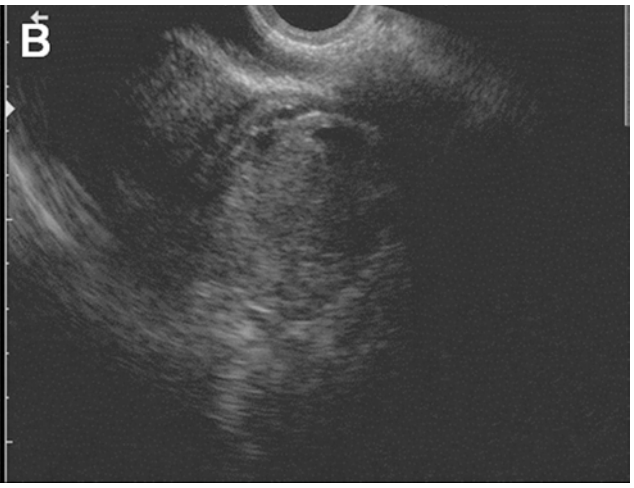

Fig. 2A

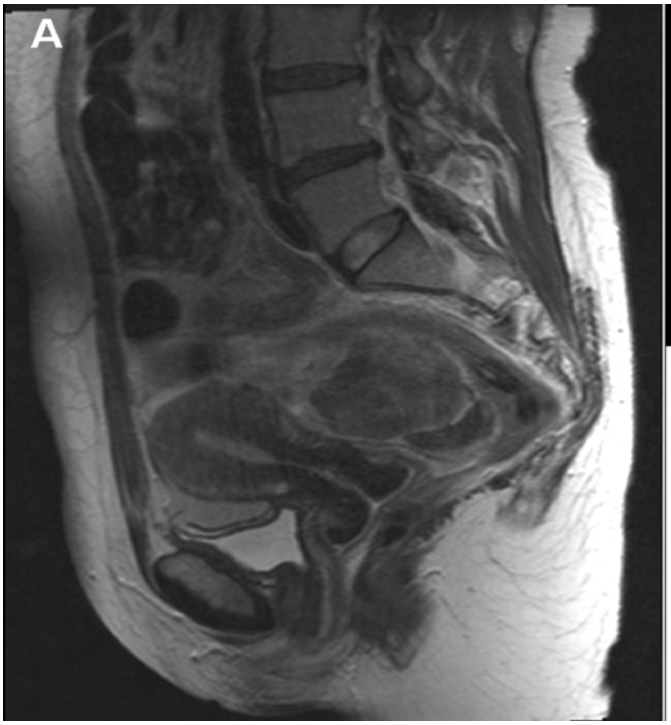

Fig. 2B

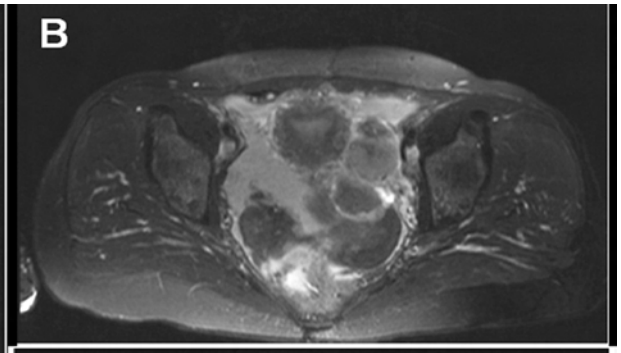

Fig. 2C

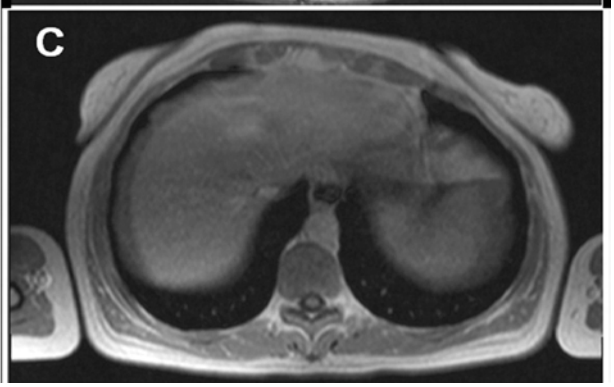

Figure 1. — Ultrasound images during admission to the hospital. A) Free fluid and blood clot in Douglas pouch. B) Left ovary with blood clot.
Figure 2. — MRI images during admission to the hospital. A) Sagittal section of pelvis, left ovary with blood clot. B) Transversal section of pelvis, with pelvic free fluid. C) Perihepatic and perisplenic blood.

diameter of 5.8 x 4.0 cm. Another formation (3.8 x 3.5 cm in diameter) with the same MRI characteristics, was located parasagittally on the right side in Douglas's pouch corresponding to the blood clots. Perihepatic and parasplenic free hemorragic fluid was verified as well (Figures 2A, B, and C). These finding confirmed the hematoperitoneum caused by ovulation, which represents the condition that is usually managed surgically.

Since the patient was hemodynamically stable, the decision was made to treat the patient conservatively. After the initial administration of cryoprecipitate (20 IU), therapy was continued with Haemate P 2000 IU / 24 hours i.v. in combination with iron supplements. The laboratory analysis included CBC, PT, PTT, and fibrinogen performed on a daily basis. The fourth day from the beginning of therapy, the VFW was 64%, and F VIII 133%, and the day after VFW was 80%, and F VIII was 114%. On the sixth day, the value of VWF decreased to 32%, and on day eight, it was 16%. The value of hemoglobin increased, and on day 11 it wa 125 g / l. Since vital parameters, clinical, and CBC findings were stable, the substitution therapy was suspended. Two days later, the value of VFW was zero percent again. The control ultrasound exam showed that there was no free liquid around the liver and spleen, while the amount of pelvic free fluid was decreased. The ovary and the clot around the ovary were the same size as previously measured. The final ultrasound exam before discharge, showed a significant

Fig. 3A

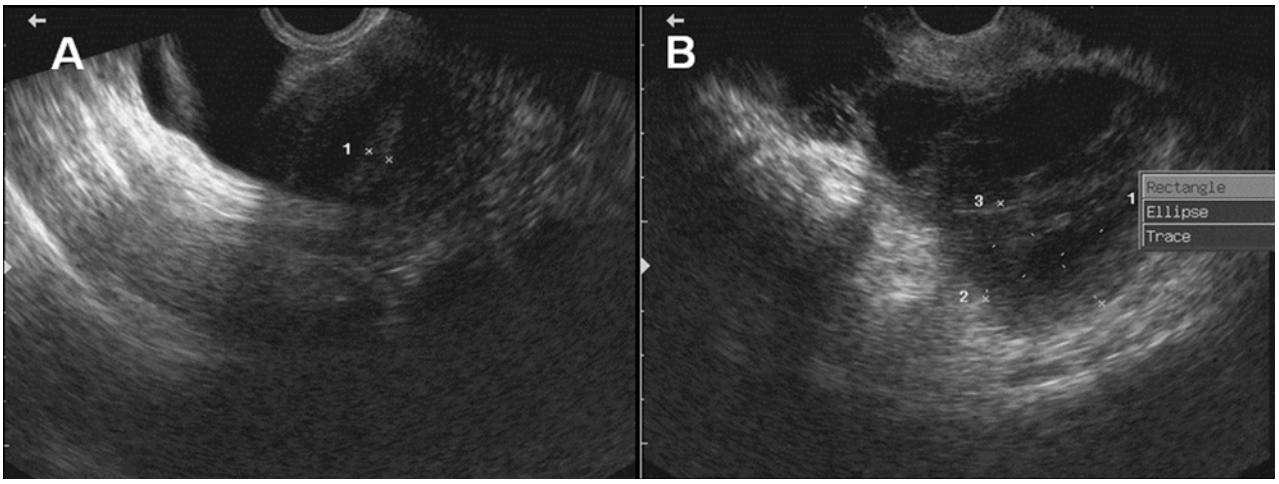

Fig. 3B

Figure 3. — Ultrasound images after treatment. A) Uterus with thin endometrium. B) Left ovary with no free fluid.

improvement (Figures 3A and B). The patient was discharged home with oral contraceptive therapy. The contraceptive therapy was continued from the first day of next menstrual period for another three months. The patient was in good clinical condition during regular monthly follow ups throughout a period of three months.

Discussion

VWD is caused by the abnormality of VWF, which plays an important role in hemostasis. It is the most frequent form of inherited abnormality of hemostasis. The main manifestation of VWD is a mucocutaneous hemorrhagic syndrome. Early diagnosis is very important to avoid hemorrhagic complications, especially if the surgical procedure is planned or inevitable [7]. The degree of the VWF defect determines the severity of spontaneous bleeding [8]. In these patients, prophylactic treatment is required in order to prevent excessive bleeding following surgery [8]. It is usually short-term prophylaxis used to prevent imminent postoperative complications [8]. Patients with severe forms of the VWD may have frequent hemarthroses, especially when a factor VIII (FVIII) levels are below 10 IU / dL, recurrent gastrointestinal (GI) bleeding, and in children who have epistaxis frequently can cause anemia [9]. In these patients, long-term prophylaxis with VWF / FVIII concentrates should be the matter of choice, rather than just treatment of bleeding episodes [9].

Although hematoperitoneum following ovulation is rarely clinically significant, in women with congenital or acquired bleeding disorders, it may lead to life-threatening hemorrhage [6, 10]. It is more common in patients with severe bleeding disorders, such as afibrinogenemia, type 3 of VWD, or in patients undergoing oral anticoagulation therapy [5]. Hemoperitoneum due to a gynecological disease in patients with VWD can be a very acute condition that requires emergency surgery. In cases of massive hematoperitoneum, surgical interventions, such as adnexectomy or oophorectomy, are usually performed [6, 11]. However, surgery may represent the additional risk for these patients, and this was one of the reasons why the authors decided to proceed with conservative treatment.

Conservative treatment in the present case was also determined by the patient's hemodynamic stability. Initial administration of cryoprecipitate was substituted with Haemate P i.v. (2000 IU/24h). Haemate P is the widely used VWF/FVIII concentrate due to its high VWF : FVIII ratio [12]. Federici *et al*. showed in a cohort study, an excellent to good clinical response with VWF / FVIII concentrates in 97% of bleeding episodes and in 99% of surgical procedures in patients with VWD [13]. Conservative management with blood product and factor concentrate should be considered when it is possible to avoid surgery [11]. Study of Payne JH, *et al*. demonstrated that recurrent bleeding episodes following ovulation may be conservatively treated and prevented by ovulation suppression [11]. Although the nature of VWD is heterogeneous, the concentration of zero percent VWF, as the patient had, is very rare and almost accidental. The patient was observed by the hematologist, and during therapy, the maximal value of VFW was 80% and decreased over the following eight days, while hemoglobin levels increased. Single daily doses of Haemate P in this case proved to be sufficient, both as potential surgery prophylaxis and as a therapy. After achieving a stable condition of the patient, treatment was continued with long-term hemorrhagic prophylaxis by using oral contraceptive pills. Oral contraceptives are the treatment of choice in congenital bleeding disorders to control ovulation-related hemoperitoneum [11, 14]. Since the treatment with Haemate P can lead to thromboembolic complications, it is very important to perform a pharmacokinetic study in order to strictly tailor doses of VWF / FVIII concentrates [12, 15].

The present is a unique case of massive hematoperitoneum treated conservatively in a woman with very severe VW disease (0% VWF). The patient was clinically stable all the time, and the treatment was conducted with

single daily dose of 2000 IU i.v. of Haemate P, which proved to be sufficient. Massive hemoperitoneum due to ovulation is a serious complication for women with VWD, and usually leads to surgery. This case report showed that conservative management could be a method of choice even in patients with a severe form of VWD, if they are hemodynamically stable. This can be achieved by using VWF / FVIII concentrates and oral contraceptive pills to prevent recurrent bleeding episodes that might appear after ovulation.

References

[1] Rodeghiero F., Castaman G., Dini E.: "Epidemiological investigation of the prevalence of von Willebrand's disease". *Blood,* 1987, *69,* 454.

[2] Kujovich J.L.: "von Willebrand disease and pregnancy". *J. Thromb. Haemost.,* 2005, *3*, 246.

[3] Sadler J.E., Mannucci P.M., Berntorp E., Bochkov N., Boulyjenkov V., Ginsburg D. *et al.*: "Impact, diagnosis and treatment of von Willebrand disease". *Thromb. Haemost.,* 2000, *84,* 160.

[4] Terzic M., Stimec B., Maricic S.: "Laparoscopic management of consecutive ovarian pregnancy in a patient with infertility". *Zentralbl. Gynakol.,* 2001, *123*, 162.

[5] Meschengieser S.S., Alberto M.F., Salviu J., Bermejo E., Lazzari M.A.: "Recurrent haemoperitoneum in a mild von Willebrand's disease combined with a storage pool deficit". *Blood Coagul. Fibrinolysis,* 2001, *12*, 207.

[6] Cetinkaya S.E., Pabuccu E.G., Ozmen B., Dokmeci F.: "Recurrent massive hemoperitoneum due to ovulation as a clinical sign in congenital afibrinogenemia". *Acta Obstet. Gynecol. Scand.,* 2011, *90,* 192.

[7] Boehlen F., Robert-Ebadi H., de Moerloose P.: "Von Willebrand disease: a common and unrecognized bleeding disorder". *Rev. Med. Suisse,* 2007, *3*, 346.

[8] Franchini M.: "Surgical prophylaxis in von Willebrand's disease: a difficult balance to manage". *Blood Transfus.,* 2008, *6,* 33.

[9] Federici A.B.: "Prophylaxis of bleeding episodes in patients with von Willebrand's disease". *Blood Transfus.,* 2008, 6, 26.

[10] Hoffman R., Brenner B.: "Corpus luteum hemorrhage in women with bleeding disorders". Women's Health (Lond. Engl.), 2009*, 5,* 91.

[11] Payne J.H., Maclean R.M., Hampton K.K., Baxter A.J., Makris M.: "Haemoperitoneum associated with ovulation in women with bleeding disorders: the case for conservative management and the role of the contraceptive pill". *Haemophilia,* 2007, *13,* 93.

[12] Auerswald G., Kreuz W.: "Haemate P/Humate-P for the treatment of von Willebrand disease: considerations for use and clinical experience". *Haemophilia,* 2008, *14*, 39.

[13] Federici A.B., Barillari G., Zanon E., Mazzucconi M.G., Musso R., Targhetta R. *et al.*: "Efficacy and safety of highly purified, doubly virus-inactivated VWF/FVIII concentrates in inherited von Willebrand's disease: results of an Italian cohort study on 120 patients characterized by bleeding severity score". *Haemophilia,* 2010, *16,* 101.

[14] Girolami A., Lombardi A.M., Candeo N., Scarparo P., Paternoster A.: "Control of ovulation-induced hemoperitoneum by oral contraceptives in a patient with congenital hypoprothrombinemia and in another with congenital factor V deficiency". *Acta Haematol.,* 2008, *119*, 236.

[15] Batlle J., Lopez-Fernandez M.F., Fraga E.L., Trillo A.R., Perez-Rodriguez M.A.: "Von Willebrand factor/factor VIII concentrates in the treatment of von Willebrand disease". *Blood Coagul. Fibrinolysis,* 2009, *20,* 89.

Address reprint requests to:
M. TERZIC, M.D., Ph.D.
Department of Gynaecology and Obstetrics
Faculty of Medicine, University of Belgrade
Visegradska 26
11000 Belgrade (Serbia)
e-mail: terzicmilan@yahoo.co.uk