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Case Report

Recurrent Hemoperitoneum after Oocyte Pick-Up in an IVF Patient with Von Willebrand Disease May be Prevented with a Combination of Factor VIII and Von Willebrand Factor -

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ABSTRACT

Background: Hemoperitoneum is an uncommon complication after Transvaginal Ultrasound-Guided Oocyte Retrieval (TUOR). There are some reports linking hemoperitoneum with coagulation disorders after either spontaneous ovulation or TUOR. Von Willebrand Disease (vWD) is the most common inherited bleeding disorder present in 1% of the population.

Case: A 35-year-old woman was referred to our assisted reproduction unit for a 3-year history of primary infertility. She had no relevant medical or surgical history, except for a myomectomy by laparotomy that was uneventful with no postoperative complications.

The patient underwent two cycles of IVF and after each TUOR had an episode of hemoperitoneum. Thus, we conducted hematological analysis. This indicated that the patient had type 1 vWD. However, test results were not completely conclusive.

Nevertheless, given her history, and seeking to avoid a third episode of hemoperitoneum, we decided to administer a combination of factor VIII and von Willebrand factor 30 minutes before the third TUOR, we do not detect complications after the procedure.

Conclusion: Although indications for treatment were not clear, in our opinion, the good clinical outcome and lack of associated risks make administration of this medication highly recommendable in patients with symptomatic vWD undergoing IVF.

INTRODUCTION

To our knowledge, there are no previous reports of prophylactic treatment of vWD patients with factor VIII and Von Willebrand Factor (VWF) before Transvaginal Ultrasound Oocyte Retrieval (TUOR). After TUOR, the vaginal hemorrhage is not uncommon (8.6%) although the loss of > 100 ml of blood is less frequent (0.8%) [1-3]. Hemoperitoneum (0.06-0.08%) and puncture of iliac vessels (0.04%) are much more infrequent [1,4]. Von Willebrand Disease (vWD) is the most common inherited bleeding disorder present in 1% of the population, although only approximately 1% of these individuals are symptomatic.

vWD disease is classified in different categories. Type 1 includes partial quantitative deficiency, type 2 includes qualitative defects, and type 3 includes virtually complete deficiency of VWF. VWD type 2 is divided into four secondary categories.

Type 1 is an autosomal dominant disease and it is the most common (75% aproximately). Although there have been some reports linking coagulopathies with hemoperitoneum after oocyte pick-up [5], there are few cases concerning hemoperitoneum in individuals with Von Willebrand disease [4].

CASE REPORT

A 35-year-old woman with a 3-year history of primary infertility was referred to our assisted reproduction unit. The patient had regular menstrual cycles and presented mild dysmenorrhea.

Two years earlier, pelvic ultrasound revealed two subserosal myomas (4 and 6 cm) and an endometrioma (2.5 cm) in the left ovary. Patent normal tubes were seen on hysterosalpingography. Her partner presented oligoasthenoteratospermia. Laparotomy was performed by her general gynecologist and both myomas were removed. Surgery was uneventful. No blood transfusions were needed.

Subsequently, the patient underwent her first cycle of *In Vitro* Fertilization (IVF) in a private clinic (data shown in table 1). About 12 hours after TUOR, she presented to the emergency department of our hospital with abdominal pain and physical discomfort. The hemoglobin level was 7.4 g/dl and an ultrasound scan revealed moderate hemoperitoneum. The patient received 3 units of red blood cell concentrate but did not require any surgical treatment. After 5 days she was discharged.

Before any further reproductive treatment, hematological analysis was conducted, and this ruled out thrombophilic conditions. Values of antithrombin III, S and C proteins, factor V Leiden and prothrombin mutations were within normal ranges.

Table 1: Summary of the characteristics of the three cycles of *In Vitro* Fertilization (IVF)

IVF cycle no.	Ovarian Stimulation	Maximum estradiol level, pg/ml	Metaphase II oocytes retrieved	Hemoperitoneum	Prophylactic administration of factor VIII-von Willebrand factor
1	Cetrorelix + 2475 IU FSH	2153	6	Yes; Hb 7.4 g/dl	No
2	Cetrorelix + 1650 IU FSH + 1650 IU HMG	3025	12	Yes; Hb 8.3 g/dl	No
3	Cetrorelix + 1650 IU FSH + 1650 IU hMG	2190	5	No	Yes

hMG: Human Menopausal Gonadotropin; FSH: Follicle-Stimulating Hormone

Fifteen months later, our patient underwent her second IVF cycle in our center (Table 1).Ten hours after the oocyte retrieval, she was admitted to the emergency department with abdominal pain. This time the hemoglobin level was 8.3 g/dl and the ultrasound showed mild hemoperitoneum. Neither surgery nor transfusion was needed and the patient was discharged after 4 days.

The patient was referred for a more complete hematological analysis, which was performed at another hospital. The coagulation testing only revealed a lower than normal ristocetin-induced platelet aggregation (16.9%; normal 50-100%). The other parameters, including levels of factor VIII and VWF antigen were normal. Based on these results, the hematologists that evaluated the case made the diagnosis of type 1 vWD.

We decided to ask for a second opinion and referred her to our hospital's hematologists. New basic coagulation testing was conducted, and results were normal. Testing using collagen and epinephrine indicated abnormal platelet function (> 300 s vs. normal time of 170 s), but completely normal platelet aggregation. Factor dosage required indicated slightly low levels of von Willebrand factor: functional VWF 32.3% and VWF antigen 41% (normal 50-150%). These outcomes were not conclusive for the diagnosis of vWD, but due to the patient's history of hemoperitoneum after previous TUORs, we decided to recommend the administration of prophylactic treatment

before subsequent procedures.

With this information available, the patient underwent her third IVF cycle (Table 1). On this occasion, we conducted a blood test the day before the oocyte retrieval to evaluate coagulation. Once again, results of the coagulation testing were normal. The level of functional VWF was slightly low (42.3%) and that of VWF antigen (57%) was normal; both levels were somewhat higher than the basal values, this probably being attributable to the hormonal treatment administered.

Given the complications after the previous TUORs and the findings in the coagulation testing, we decided to administer intravenously a combination of factor VIII (1000 U) and VWF (1200 U) (Fanhdi, Grifols, Barcelona) 30 minutes before the puncture. Following this third TUOR, no incidents were reported, in the following hours or days after the procedure.

DISCUSSION

Hemoperitoneum is a very uncommon complication of TUOR. Reported frequencies range from 0.06 to 0.08% [1-3]. Regarding vWD, which affects 1% of the population (1% of them being symptomatic, that is 1/10,000), and has been reported in 1/2500 hysterectomies and 1/4000 labors [4], it is notable that there are very few reports of its diagnosis among patients undergoing TUOR.

Several reports have described hemoperitoneum after spontaneous ovulation in vWD patients [6-8]. To our knowledge, 17 patients have been reported to have episodes of hemoperitoneum in association with TUOR [1, 3], but in only one case has such an episode been associated with vWD [4].

In IVF stimulation cycles, it has been reported that increases in estradiol and factor VIII during IVF are paralleled by an increase in VWF antigen and activity, and a decrease in circulating ADAMTS13 antigen and activity, respectively [9]. Such changes are consistent with the well-known increased risk of thrombosis in patients undergoing IVF [9]. One could speculate that in some cases it could in some way compensate for the increased bleeding risk in some vWD patients. In agreement with these results, in the present case, we can demonstrate that all of the parameters of the coagulation improved in the test that was performed the day before the oocyte retrieval, compared with her results under basal conditions.

Concerning prophylactic treatment with a combination of factor VIII (1000 U) and VWF (1200 U) our patient did not have a further episode of hemoperitoenum after this treatment. We administered a dose of 20 U/kg. The known risks associated with this type of treatment are only very infrequent allergic reactions (very rare after a single dose). Hence, in our opinion, although the indications for treatment were not clear and one cannot know what would have happened if we had not given the treatment, her good clinical outcome and the minimal associated risks make administration of this medication highly recommendable in patients with symptomatic vWD undergoing IVF.

To sum up, we recommend hematological analysis prior to IVF in patients with a history of bleeding or hemoperitoneum after TUOR. If vWD is detected, prophylactic treatment with a combination of factor VIII and VWF should be considered.

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