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PREVENTION OF HEMOPERITONEUM DURING OVULATION BY ORAL CONTRACEPTIVES IN WOMEN WITH TYPE III VON WILLEBRAND DISEASE AND AFIBRINOGENEMIA. CASE REPORTS

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The follicle ruptures at the time of ovulation and fills with blood, forming a corpus hemorrhagicum. Minor bleeding from the follicle into the abdominal cavity may cause peritoneal irritation and, when it occurs in a patient with a defect of primary hemostasis, hemoperitoneum can occur. Von Willebrand disease and afibrinogenemia are two important bleeding disorders in which both primary hemostasis and coagulation are involved. Bleeding during ovulation is one major clinical complication in women with these disease. We have studied three patients with this hemorrhagic complication. Our data show that oral contraceptives are an effective way to avoid hemoperitoneum.

KEY WORDS: Von Willebrand disease, oral contraceptives, afibrinogenemia.

Von Willebrand disease (vWD) is an autosomal dominant or recessive bleeding disorder characterized by the absence or low levels or abnormalities of plasma von Willebrand factor (vWF) [1-3]. The vWF defects result in a secondary defect of factor VIII (the protein that is deficient or defective in hemophilia), which is carried and stabilized by vWF in plasma. Afibrinogenemia, in which levels of plasma fibrinogen are unmeasurable, is a congenital bleeding disorder with autosomic recessive transmission [4]. We have studied three women with these diseases who had severe bleeding complications at ovulation. We shall describe these cases here and discuss the therapies we attempted.

METHODS

Bleeding time was carried out in duplicate, using the automatic device Simplate II (General Diagnostic, Milano, Italy) [5].

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Platelet counts were obtained with the Coulter counter (Thrombocounter-C Harpenden, DR).

Factor FVIII was assayed by a one-stage clotting technique, and plasma concentrations were expressed in units per deciliter referred to pooled normal plasma calibrated against the Second International Reference Preparation for FVIII-related Activities in plasma [6].

vWF Antigen (vWF:Ag) was measured by electroimmunoassay (EIA) and plasma concentrations were expressed as for factor VIII [7].

Ristocetin cofactor activity (Ricof) was measured by aggregation of fixed platelets and plasma concentrations were expressed as for wWF:Ag and Ricof [8,9].

Fibrinogen was assayed by the quantitative method of Clauss [10] (Fibrinogen Reagent, Hemodiagnostica Stago, Asnieres, France).

CASE 1. B.B.B. is a 26 year-old woman with severe (type III) vWD. Von Willebrand factor antigen (vWF:Ag), ristocetin cofactor activity (Ricof) and factor VIII were unmeasurable and bleeding time was very prolonged (> 30 min) but the platelet count was normal. Since childhood, all episodes of bleeding (nosebleeds, hemarthroses and dental extractions) were treated with cryoprecipitate. At age fifteen, she had menarche with severe vaginal bleeding (hematocrit 26%; Hb 8.2 g/L). Bleeding stopped after transfusion of more than 10 units of whole blood and an intravenous infusion of conjugated estrogens (20 mg premarin i.v., four times/day for three days). For about three years she took oral contraceptives (0.03 mg ethinyl estradiol; 0.15 mg levonorgestrel). The patient refused to continue this therapy and had several episodes of abdominal pain, interpreted as being due to iliopsoas hematomas. During the last episode, gynecological examination detected a poorly delineated «cul de sac» mass and severe pain on palpation of the uterus. Echography revealed intraperitoneal bleeding. The patient was treated with cryoprecipitate and transfused with red blood cells. Pain disappeared, but echography showed the mass still present. At laparotomy a hemoperitoneum was found, caused by a hemorrhagic corpus luteum in the right ovary. A wedge resection of the ovary was done after treating the patient with cryoprecipitate (7 bags per day for 6 days). The patient was then advised to resume the treatment with a combination of triphasic oral contraceptives. She continued this treatment

for three years without interruption. She then decided to suspend the therapy and had a new episode of bleeding from a hemorrhagic corpus luteum, and again the the symptoms disappeared after cryoprecipitate infusion. Since then, the patient has been taking hormonal contraceptives (triphasic formulation) without mishap.

Case 2. C.K. is 19 years old. This patient has severe (type III) vWD, with unmeasurable levels of Ricof, vWF:Ag and factor VIII, a bleeding time of more than 30 min and a normal platelet count. The patient had several bleeding episodes in her childhood for which she was treated with fresh frozen plasma, cryoprecipitate and red blood cell transfusions. When she was fourteen years old, she had a hemorrhagic menarche and was transfused. After treatment with cryoprecipitate and blood, she developed high levels of an antibody against vWF. Recently it has been demonstrated that this patient has a complete deletion of the vWF gene [11].

At the age of fifteen, she had hemoperitoneum. Pelvic echography showed a retrouterine dishomogeneous mass and a large cyst on the left ovary. Explorative laparotomy was not possible because of an allergic reaction to the infusion of cryoprecipitate, causing hypotension and dyspnea. She was then treated by intravenous administration of conjugated estrogens (20 mg premarin i.v. for 3 days followed by 1.25 mg/day orally for ten days) plus medroxyprogesterone acetate (10 mg/day for two weeks). Echography was then performed every week and showed a reduction of the mass and the cyst after one month, and resolution after 9 months. During this period the patient was treated with a combination of oral contraceptives (0.03 mg ethinyl estradiol plus 0.15 mg levonorgestrel). After suspension of the therapy she had abdominal pain and hemoperitoneum. She was treated with an antifibrinolytic agent (tranexamic acid) and conjugated estrogens. Oral contraceptive therapy was then re-established, and she has had no further trouble.

Case 3 T.N., 22 years old, has congenital afibrinogenemia with unmeasurable levels of fibrinogen, a bleeding time of 18 min, and a normal platelet count. At the time of first observation the patient described a history of postoperative, traumatic and spontaneous bleeding. Menarche, age thirteen, was complicated by bleeding and anemia, which required treatment with fresh-frozen plasma. When she was fifteen, she was admitted to a different hospital for a hemoperitoneum. At that time only the peritoneal blood was removed, since the source of bleeding was not identified. Five months later she was admitted to the same hospital for another episode of hemoperitoneum. This time a hemorrhagic corpus luteum was found on the right ovary, and a wedge resection was performed. The two laparotomies were managed without mishap by infusing fresh-frozen plasma. One year later the patient was admitted to our istitution for emergency surgery because of another hemoperitoneum. Her hematocrit was 29%. The patient was treated with 5 g fibrinogen to correct the hemostasis defect and laparatomized with a wedge resection of the left ovary. The patient was dismissed on oral contraceptive therapy (0.03 mg etinyl estradiol, 0.15 mg levonorgestrel) which she is still taking.

Discussion

In vWD and afibrinogenemia, menorrhagia is the most important gynecological problem, and post-partum hemorrhage can be an obstetric complication [12]. Bleeding during ovulation is another clinical complication in women with severe vWD disease or afibrinogenemia. As seen from our cases, a bleeding follicle can cause hemoperitoneum. Since patients with type III vWD and afibrinogenemia are totally or partially unresponsive to the non-transfusional agent desmopressin (DDAVP) [13], blood products such as cryoprecipitate and fresh-frozen plasma, which contain factor VIII, vWF and fibrinogen, are the mainstay of treatment for acute bleeding episodes. Using these fractions, our cases with hemoperitoneum could be managed conservatively. Because of their hemostatic action, conjugated estrogens were apparently a successful alternative to blood products in our patient with severe vWD complicated by alloantibodies who could not be treated with plasma fractions. Conjugated estrogens do not influence the circulating levels of vWF, and their beneficial effect is not due to any effect on platelet or hormonal functions. Therefore, the mechanism of action is not known [14]. Since hemoperitoneum from bleeding follicles tended to recur in our patients, we attempted to prevent it by putting them on long-term oral contraceptive therapy. These favourable results were probably achieved because oral contraceptives block ovulation, prevent the formation of a corpus luteum and render the endometrium less susceptible to extensive bleeding at the time of menstruation. Long-term treatment with contraceptives is obviously more practical and safer than administration of cryoprecipitate or other blood products at the time of ovulation or menstruation, because these products carry a risk of infecting the patients with the hepatitis virus or the human immunodeficiency virus. When one of these young women wishes to suspend the contraceptives in order to become pregnant, we will evaluate the development of the follicle by serial echography and hormonal surveillance every day to establish the time of ovulation, and at ovulation we will give replacement therapy for two or three days to prevent follicular bleeding. From our experience throughout pregnancy and up to delivery with other patients having type I and II von Willebrand disease [12], these women are unlikely to have hemorrhagic complications. Complications at the time of delivery can be handled or prevented with blood products or desmopressin.

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