Acquired haemophilia due to factor VIII inhibitors in ovarian hyperstimulation syndrome: Case report

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A 31-year-old nulligravida woman developed an acquired factor VIII inhibitor associated with severe ovarian hyperstimulation syndrome (OHSS). She developed haematouria, ecchymosis, and intramuscular bleeding following the severe OHSS. Laboratory examinations showed a markedly prolonged activated partial thromboplastin time and a low level of factor VIII activity. Treatment with prothrombin complex concentrate and factor VIII inhibitor bypassing agent was successful in reducing the inhibitor so that she delivered a healthy baby via spontaneous vaginal delivery. Acquired haemophilia is a life-threatening disorder. This is the first case report of acquired haemophilia in OHSS.

Key words: acquired haemophilia/assisted conception/factor VIII inhibitor/OHSS

Introduction

Acquired haemophilia caused by factor VIII inhibitors is a rare disorder but is a serious cause of haemorrhage. Factor VIII inhibitors can appear spontaneously in otherwise normal people. Factor VIII inhibitors occur in 0.2–1.0 individuals per million people per year (Lottenberg et al., 1987). Acquired haemophilia is associated with autoimmune diseases, malignancy, dermatological disorders, drug interactions and the postpartum period. Acquired haemophilia may occur at any time in pregnancy but occurs more frequently in the postpartum period. The characteristics of ovarian hyperstimulation syndrome (OHSS) are cystic enlargement of the ovaries with assisted conception and fluid loss from capillaries into the extravascular compartment. The mechanisms on the development of OHSS are still not clear. This is the first case report, to our knowledge, of acquired haemophilia in OHSS.

Case report

A 31-year-old nulligravida woman with a history of infertility secondary to severe male factor infertility underwent her first cycle of IVF and ICSI. She received luteal-phase GnRH for down-regulation and then stimulation with hMG source. Pituitary down-regulation with transnasal buserelin acetate (Suprefact; Hoechst, Turkey) 300 µg three times daily was followed by ovarian stimulation with a daily dose of 150 IU of hMG i.m. for 8 days. After 12 days of ovarian stimulation, the patient developed 20 pre-ovulatory follicles ranging in diameter from 18–21 mm. Her peak estradiol level at the time of the hCG injection was 4000 pg/ml. A dose of 10 000 IU of hCG (Profase; Serono Laboratories, Norwell, MA, USA) was administered subsequently, and standard transvaginal oocyte aspiration under ultrasound guidance was performed 36 h later. Twenty oocytes were retrieved. Sixteen of the oocytes were fertilized by ICSI. Three embryos were transferred into the uterine cavity 3 days after their retrieval. Luteal phase support was provided by 5000 IU hCG 3 times every other day.

Three days after embryo transfer, the patient complained of acute abdominal distension, nausea and vomiting. Her systolic blood pressure had dropped to 50 mmHg, and her diastolic blood pressure and pulse rate were undetectable. Transvaginal ultrasound revealed bilateral ovarian enlargement and massive ascites. Laboratory studies disclosed the following values: white blood cell count, 32.5 × 10³/mm³; haematocrit, 48.5%; and haemoglobin, 16.7 g/dl. These signs and symptoms suggested severe OHSS. The patient was admitted to our hospital for observation and treatment.

On admission to our intensive care unit, the patient received a large volume of plasma expander and dopamine hydrochloride to correct her hypovolaemic shock. She received 3000 ml of plasma protein fraction for 6 days and 25 g of human serum albumin for 2 days together with furosemide to prevent acute renal failure. She recovered from the hypovolaemic shock on hospital day 14.

Her pregnancy test was positive 17 days after embryo transfer. Her abdominal distension and dyspnœa became more
severe. Abdominal paracentesis and thoracentesis were performed, and 3600 ml of ascitic fluid and 600 ml of pleural effluent were drained respectively.

On hospital day 29, the symptoms of OHSS lessened and the patient gradually improved, but she developed gross haematuria and ecchymosis on her right leg. Laboratory values at this time were haemoglobin, 8.0 g/dl; platelet count, 612 × 10⁹/l; prothrombin time (PT), 12.3 s (control, 13.7 s); activated partial thromboplastin time (aPTT), 95.5 s (control, 34.4 s); and bleeding time, 5.0 min (normal reference, 2–7.5 min). Haematological evaluation revealed the presence of a clotting inhibitor. The patient had a factor VIII level of 2.5% (normal reference, 60–145%). The test result for factor VIII inhibitors was positive, the inhibitor level was 10.0 Bethesda units (BU). Test results of rheumatoid factor, antinuclear antibody and anticardiolipin IgG were all normal or negative. We made a diagnosis of acquired haemophilia.

The patient was given an i.v. dose of 50 IU/kg of factor VIII inhibitor bypassing agent (FEIBA) to achieve haemostasis. After she received the FEIBA therapy, both the amount of gross haematuria and the size of the ecchymosis decreased. Her factor VIII inhibitor titre gradually decreased and then disappeared. Her subsequent hospital stay was uneventful, and the patient was discharged 10 weeks after her initial admission.

The patient’s pregnancy was complicated by pre-term labour at 32 weeks gestation culminating in the spontaneous vaginal delivery of a healthy boy. On the day of delivery, coagulation studies showed an aPTT of 44.0 s (control, 36.7 s), a factor VIII level of 2.5% (normal reference, 60–145%). The test result for factor VIII inhibitors was positive, the inhibitor level was 10.0 Bethesda units (BU). Test results of rheumatoid factor, antinuclear antibody and anticardiolipin IgG were all normal or negative. We made a diagnosis of acquired haemophilia.

Discussion

To our knowledge, this is the first reported case of acquired haemophilia in OHSS. Acquired haemophilia occurs as a result of the spontaneous development of autoantibodies against factor VIII (Bossi et al., 1998). About 10% of these cases have been reported during the third trimester of pregnancy or during the postpartum period, but why this occurs is uncertain (Morrison et al., 1993). Acquired haemophilia should be suspected in postpartum or pregnant patients who haemorrhage for no apparent cause and who have no history of bleeding disorders. These patients can present with severe life-threatening bleeding episodes that result in a high mortality rate. (Kashyap et al., 2001).

OHSS, which occurs in ~1–10% of the IVF cycles and in <4% of cycles for ovulation induction, is the most serious complication of assisted conception (Myrianthefs et al., 2000). Severe OHSS is a life-threatening condition and continues to be the most serious complication of controlled ovarian stimulation. Severe OHSS is further defined by renal failure, thromboembolic phenomena and adult respiratory distress syndrome. The mechanisms for the development of OHSS are still not clear. The characteristic features of OHSS are cystic enlargement of the ovaries and fluid loss from capillaries into the extravascular compartment leading to dehydration, hypovolaemia, haemoconcentration, oedema, ascites, hydrothorax, dyspnoea, electrolyte imbalance, abdominal distension and pain. These findings may be due to increased capillary permeability and new capillary vessel formation (Tollan et al., 1990). Haemorrhage is a rare symptom in OHSS.

Most patients with acquired haemophilia present with spontaneous bleeding into muscle or soft tissue or with ecchymoses. Bleeding is usually severe and occurs concurrently at several different anatomical sites (Morrison and Ludlam, 1995). Lottenberg et al. reported that they had observed two deaths directly due to severe bleeding associated with acquired haemophilia (Lottenberg et al., 1987). The aPTT is greatly prolonged, but the bleeding time and platelet count are normal in patients with acquired haemophilia. Clotting factor VIII activity decreases and the factor VIII inhibitor level increases. Because of a delay in diagnosis, patients with acquired factor VIII inhibitor have a greater risk of death due to uncontrolled haemorrhage than do haemophilia patients with inhibitors. Mortality due to haemorrhage in these cases varies between 12 and 22% in some reports (Green, 1999).

The primary aim of medical management of patients with acquired haemophilia is to control the acute bleeding. Factor VIII concentrate may reverse the effects of acquired haemophilia in mild cases where inhibitor titres are low. If a patient has a higher titre of factor VIII antibodies and severe bleeding occurs, then the patient must be treated with recombinant factor VIII or, alternatively, FEIBA, an activated prothrombin complex concentrate (PCC) that includes factor IX and activated factor VIIa. FEIBA may be beneficial (Morrison et al., 1993; Shobeiri et al., 2000), but its haemostatic effect is not well understood, and the safety of FEIBA therapy in pregnant women has not yet been established. Some concerns exist regarding the risk of adverse effects such as disseminated intravascular coagulation, acute myocardial infarction or viral infection, particularly hepatitis B and C.

The secondary aim of medical management is to accelerate the disappearance of the factor VIII inhibitors. This may be achieved with immunosuppressive drugs such as corticosteroids, cyclophosphamide or azathioprine, and immunotherapy (Shobeiri et al., 2000).

In this case, we could have avoided the OHSS by not using hCG during the luteal phase, because this patient had three known risk factors for OHSS: estradiol slope, estradiol level and number of oocyte retrieval. Also the luteal phase administration of human hCG was associated with a higher incidence of severe OHSS than was supplementation with progesterone alone (McClure et al., 1992). Progesterone is the product of choice as it is associated with a lower incidence of OHSS. The most recent studies are very clear regarding the treatment choice of the luteal supplementation with or without risk factor of OHSS by progesterone, because of no differences in outcomes (Penzias, 2002).

Acquired haemophilia is a life-threatening disorder. Low levels of factor VIII inhibitors have been detected in 17% of healthy individuals who have no clinical symptoms and no other biological abnormalities (Algiman et al., 1992). It is worthwhile to measure factor VIII activity and its inhibitor in patients with bleeding and a prolonged aPTT but with a normal
bleeding time and a normal platelet count, even in patients with OHSS. Further study is needed to understand the role of acquired haemophilia in OHSS.

References


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