CASE REPORTS

Moderate ovarian hyperstimulation syndrome complicated by deep cerebrovascular thrombosis

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This report describes two cases that developed moderate ovarian hyperstimulation syndrome (OHSS) without evidence of haemoconcentration. Both patients developed serious cerebrovascular thrombosis resulting in hemiparesis, and recovered after treatment with anticoagulants. This report emphasizes that other factors may contribute to vascular thrombosis, and illustrates that cerebrovascular accidents may complicate even moderate OHSS.

Key words: haemoconcentration/IVF/moderate OHSS/ovulation induction/vascular thrombosis

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of ovulation induction. In severe forms, the syndrome is characterized by ovarian enlargement, ascites, electrolyte imbalance, hypovolaemia and haemoconcentration (Schenker and Weinstein, 1978).

During the past 2 decades, there have been several reports of thromboembolism as a complication of severe OHSS attributed to the associated haemoconcentration (Mozes et al., 1965; Rizk et al., 1990; Fournet et al., 1991; Heignett et al., 1995). This paper reports two unusual cases in which the patients developed serious cerebrovascular accidents following induction of ovulation for in-vitro fertilization (IVF), which were associated with moderate OHSS only without evidence of haemoconcentration.

Case reports

Case 1

A 33 year old woman presented with 10 years of primary infertility initially due to an ovulatory factor, but later complicated by a tubal factor following bilateral ovarian wedge resection surgery. The patient underwent our standard long gonadotrophin-releasing hormone agonist (GnRHa)/human menopausal gonadotrophin (HMG) protocol (Aboulghar et al., 1994). HMG 150 IU per day was administered i.m. for 5 days, after which the dose was individualized according to the ovarian response. A total of 24 ampoules of HMG was given. The oestradiol concentration reached 2100 pg/ml and the number of follicles ≥16 mm in diameter was 12. Injection of 10 000 IU of human chorionic gonadotrophins (HCG) was performed and oocyte recovery took place 36 h later. In all, 14 oocytes were collected, 10 of which became fertilized. Four embryos were transferred to the uterus 48 h later and five embryos were cryopreserved. Progesterone suppositories, 200 mg, were given intravaginally twice daily for luteal phase support (Hoechst, Main, Germany).

One week later, the patient complained of mild abdominal distention and nausea. Clinical examination revealed normal vital signs. The pulse was 80/min and its volume was full, the blood pressure was 110/80 mmHg and the patient indicated that she was passing the usual volume of urine. Abdominal examination revealed a lax but slightly distended abdomen. There was no tenderness or guarding. Transabdominal ultrasound revealed moderately enlarged ovaries (to 7 cm diameter each) with a minimal amount of ascitic fluid. The haematocrit was 38% and the white cell count was 103 × 103/µl. The haemoglobin concentration (Hb) was 12.1 g/dl and the prothrombin time was normal and the volume of urine was adequate. A clinical diagnosis of cerebrovascular thrombosis was suspected, and a brain computed axial tomography (CAT) scan revealed a hypodense cortical area, with no mid-line shift denoting the presence of acute infarction. Intravenous heparin (5000 IU every 4 h) was immediately initiated and 3 l of Ringer’s solution was administered every 24 h. The motor power of the left arm and leg improved gradually over a period of a week. Two weeks after embryo transfer, the patient menstruated. She continued to receive physiotherapy for 4 months until her motor weakness improved and she returned to work. After recovery, the patient was investigated for rare but possible causes of hypercoagulable conditions, including antiphospholipid antibodies, antithrombin III deficiency, protein C and protein S deficiency (Table I).
M phosphatidyl glycerine.

retained weak motor power and restricted mobility. The patient started to move her left leg freely. The left arm

1200 ml in the first 24 h and the neck rigidity disappeared. was encouraged to drink plenty of fluids. Urine output was

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improved dramatically. The patient became fully conscious

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solution and glucose 5% every 24 h. IV heparin 5000 IU every

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days later, the patient was referred to the hospital. She was

complained of nausea, vomiting and dizziness. She did not

85043, USA). Three days after embryo transfer, the patient

progesterone daily (Steris Laboratories Inc., Phoenix, AZ

total of seven oocytes was collected, all from one ovary

diameter was 16, and one of the ovaries was very high above

the uterus.

An injection of 10 000 IU of HCG was administered. A total of seven oocytes were collected, all from one ovary because the other ovary was inaccessible. Four oocytes were fertilized and three embryos were transferred to the uterus after 48 h. Luteal phase was supported by 100 mg i.m. progesterone daily (Steris Laboratories Inc., Phoenix, AZ 85043, USA). Three days after embryo transfer, the patient complained of nausea, vomiting and dizziness. She did not respond to antiemetics prescribed by her family doctor. Four days later, the patient was referred to the hospital. She was drowsy, blood pressure was 90/60 mm Hg, pulse was 100/min and temperature 36.5°C. Abdominal examination revealed mild distention. Ultrasound examination revealed enlargement of both ovaries to 7 and 8 cm diameter; 6 h after admission, she developed a convulsive fit for 30 s but recovered after receiving 10 mg of diazepam i.m. Left hemiparesis was diagnosed in the left arm and leg and motor power was lost in both. There was stiffness in the back of the neck. An urgent CAT scan revealed a well-defined wedge shaped hypodense area at the left parieto–occipital (cortical and subcortical region). A subtle minute hyperdense spot was noticed within the area; there was no mid-line shift and normal posterior fossa. A diagnosis of acute infarction was made.

The patient received 4 I of fluid in the form of Ringer’s solution and glucose 5% every 24 h. IV heparin 5000 IU every 4 h was also administered, together with mannitol 25% 150 ml every 12 h for 48 h.

Thirty-six hours after admission, the patient’s condition improved dramatically. The patient became fully conscious and well orientated, all the vital signs remained stable and she was encouraged to drink plenty of fluids. Urine output was 1200 ml in the first 24 h and the neck rigidity disappeared. The patient started to move her left leg freely. The left arm retained weak motor power and restricted mobility.

On the 3rd and 4th day after admission, improvement continued and the movements of both left leg and arm became normal. On admission, blood sugar, serum creatinine and liver enzymes had all been within the normal range. The haemoglobin was 10.2 g/dl, leukocyte count 9.2×10³/µl, the prothrombin time was normal, and the haematocrit was 30%. The patient was discharged in good health 6 days after admission. A few months after recovery, the patient was investigated for antiphospholipid antibodies, protein C and protein S deficiency and antithrombin III deficiency, and all the tests were within the normal range (Table I).

Discussion

Despite the advances in monitoring technology, OHSS remains a serious complication of ovulation induction by gonadotrophins. Fortunately, most cases are mild to moderate and have no major clinical consequences (Rizk and Aboulghar, 1991). Levy et al. (1996) described a woman with hypogonadotrophic hypogonadism who developed severe OHSS during ovulation induction with urinary follicle stimulating hormone (FSH) and HCG in the presence of low circulating oestradiol concentrations, suggesting that complete prevention of OHSS is not possible.

Vascular thrombosis is a rare but extremely serious complication of severe OHSS. Stewart et al. (1997a) reviewed the available literature on thromboembolic disease as a complication of ovarian stimulation and assisted conception technologies. A relatively large number of these cases had been reported, of which very little was known about their pathogenesis. Such cases are characterized by their particular occurrence in young women and their localization in uncommon sites, including the upper limbs and cerebral vessels (Hignett et al., 1995). Mozes et al. (1965) reported a fatal case of internal carotid artery thrombosis after HMG therapy, and Fournet et al. (1991) were the first to report a spontaneous internal jugular vein thrombosis associated with severe OHSS.

Stewart et al. (1997b) reported two cases of upper limb deep thrombosis, which occurred in unusual sites, well after the assumed peak periods of risk and without the development of OHSS. The authors stressed the need for further research to identify the pathogenesis and to elucidate the risks. Rizk et al. (1990) reported a case of middle cerebral artery thrombosis in a young woman, who recovered after an exploratory laparotomy to rule out OHSS induced intra-abdominal haemorrhage. Several sporadic case reports of vascular thrombosis after severe OHSS have also been published (Hignett et al., 1995). Moutos et al. (1997) reported a case of bilateral thrombosis of the internal jugular veins in a patient who developed severe OHSS after prophylactic albumin administration. The patient also received prophylactic heparin which was discontinued when her clinical course improved. In this case, the reason for the delay in the appearance of the thrombosis was not clear.

The aetiology of OHSS-associated thromboembolic disorders remains unclear. Aune et al. (1991) reported that ovarian stimulation for IVF induced a hypercoagulable state. They found a significant increase in fibrinogen and a reduction in AT III concentration and a significant increase in clotting time (CLT), implying a disruption in the balance of coagulation and thrombosis leading to a relative increase in coagulability.

| Table I. Basic coagulation status of the two patients after recovery |
|----------------|----------------|----------------|
|                | Patient I      | Patient II     | Reference range |
| Anti-cardiolipin IgG ELISA | 8.93 | 7.2 | 0–10 GPL |
| Anti-cardiolipin IgM ELISA | 2.89 | 3.1 | 0–7 MPL |
| Protein C      | 130            | 121            | 70–140% |
| Protein S      | 135            | 130            | 70–140% |
| Antithrombin III | 105%         | 108%          | 80–120% |

GPL = Immunoglobulin G phosphatidyl glycerine. MPL = Immunoglobulin M phosphatidyl glycerine.

Case 2

A 25 year old woman presented with 7 years primary infertility due to male factor.

The patient underwent our standard GnRHa/HMG protocol (Aboulghar et al., 1994). She received a total of 45 ampoules of HMG. The oestradiol concentration was 2800 pg/ml on the day of HCG injection. The number of follicles ≥16 mm in diameter was 16, and one of the ovaries was very high above the uterus.

An injection of 10 000 IU of HCG was administered. A total of seven oocytes was collected, all from one ovary because the other ovary was inaccessible. Four oocytes were fertilized and three embryos were transferred to the uterus after 48 h. Luteal phase was supported by 100 mg i.m. progesterone daily (Steris Laboratories Inc., Phoenix, AZ 85043, USA). Three days after embryo transfer, the patient complained of nausea, vomiting and dizziness. She did not respond to antiemetics prescribed by her family doctor. Four days later, the patient was referred to the hospital. She was drowsy, blood pressure was 90/60 mm Hg, pulse was 100/min and temperature 36.5°C. Abdominal examination revealed mild distention. Ultrasound examination revealed enlargement of both ovaries to 7 and 8 cm diameter; 6 h after admission, she developed a convulsive fit for 30 s but recovered after receiving 10 mg of diazepam i.m. Left hemiparesis was diagnosed in the left arm and leg and motor power was lost in both. There was stiffness in the back of the neck. An urgent CAT scan revealed a well-defined wedge shaped hypodense area at the left parieto–occipital (cortical and subcortical region). A subtle minute hyperdense spot was noticed within the area; there was no mid-line shift and normal posterior fossa. A diagnosis of acute infarction was made.

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Thirty-six hours after admission, the patient’s condition improved dramatically. The patient became fully conscious and well orientated, all the vital signs remained stable and she was encouraged to drink plenty of fluids. Urine output was 1200 ml in the first 24 h and the neck rigidity disappeared. The patient started to move her left leg freely. The left arm retained weak motor power and restricted mobility.

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Haemoconcentration, as determined by haematocrit, has been shown as the factor which correlates best with the severity of OHSS (Pride et al., 1990). Increased blood viscosity and coagulation factors associated with haemoconcentration are probably the main predisposing factors for venous thrombosis in these conditions (Kaaja et al., 1989).

Waterstone et al. (1992), in their case report of deep cerebral venous thrombosis, observed that although the haematocrit was elevated initially (58%), it had returned to normal by the time hemiparesis occurred. They suggested that thrombosis may have been present already at the time of admission.

It is uncertain whether thrombosis is dependent on the major changes in the steroid milieu induced by HMG stimulation or on change in the blood secondary to clinical OHSS (Schenker and Weinstein 1978).

In the two patients described in this report, the OHSS was not severe, urinary output was adequate and the haematocrit was within the normal range. Hence, haemoconcentration cannot be blamed for the development of vascular thrombosis in these two patients and other unknown factors may be responsible for this complication. Moreover, to our surprise, the basic coagulation status of both patients was normal.

Biochemical hyperoestrogenaemia may play a particular role because HMG stimulation alone can cause an increase in platelet count, fibrinogen, factor V and von Willebrand factor (Kim et al., 1981; Todorow et al., 1993).

Kodama et al. (1997) concluded that activation of the plasma kinin system occurs specifically and occasionally in OHSS patients and is associated with increased blood coagulability.

The role of increased circulatory concentrations of oestrogens on blood coagulability is not completely understood. Germond et al. (1996) speculated that the extrinsic coagulation pathway could be triggered by endothelial cell procoagulant activity. This activity is involved in the thrombogenesis associated with OHSS and seems to be independent of plasma oestradiol and progesterone concentrations. However, it was not clear if thrombosis in OHSS is dependent upon hormonal changes, vascular damage or haemostasis modification.

Based on these pathophysiological changes, the use of i.v. fluid therapy to prevent alteration in blood viscosity may be an important factor in the prevention of stasis and thrombosis. Prophylactic heparin therapy may be proposed in women with associated risk factors and should possibly continue during pregnancy. Those patients at risk include those who develop severe haemoconcentration, those with a history of vascular thrombosis and those with rare hypercoagulable conditions such as antithrombin III deficiency and protein S and protein C deficiency.

A group of patients may also exist with subtle problems in blood coagulation and a tendency toward the development of vascular thrombosis under such stressful conditions as OHSS present even to a moderate extent.

Venous thrombosis was previously reported as a late complication of OHSS anywhere between 2 and 20 weeks post-ovulation (Aurousseau et al., 1995). Hightett et al. (1995) reported a case of internal jugular vein thrombosis in a young, low risk, patient following severe OHSS, despite the fact that she received low dose prophylactic heparin. Horstkamp et al. (1996) reported a case of internal jugular vein thrombosis caused by resistance to activated protein C (APC) as a complication of OHSS. The coincident existence of OHSS and resistance to APC brings with it an increased risk of thrombosis.

Patients who present with recurrent venous thrombosis at an early age are usually affected by an inherited disorder of the anticoagulant mechanism that normally operates to prevent thrombosis formation. Kligman et al. (1995) reported a case of massive deep vein thrombosis in a patient with anti-thrombosis III deficiency following ovulation induction for IVF.

Aune et al. (1993) showed that there is enhanced sensitivity of the extrinsic coagulation system during IVF stimulation. The increase in available tissue factor caused by stimulation may be an important factor in thrombotic situations.

Kodama et al. (1995) suggested that marked leukocytosis and a higher level of activation of the fibrinolytic system may be signs of imminent thromboembolism in OHSS patients.

In conclusion, serious vascular thrombosis may develop as a complication of moderate OHSS with no haemoconcentration. The exact pathogenesis is unknown. If indicative biochemical parameters are found before actual thrombosis happens, anti-coagulants can be used for long periods to prevent severe complications.

References
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