CASE REPORT

Cortical vein thrombosis misinterpreted as intracranial haemorrhage in severe ovarian hyperstimulation syndrome

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A case of cortical vein thrombosis presenting as intracranial haemorrhage is described in a patient with ovarian hyperstimulation syndrome (OHSS) after IVF and embryo transfer. Veno-occlusive disease of the brain could appear as a haemorrhagic lesion on magnetic resonance imaging (MRI) and this made the initial diagnosis of cortical vein thrombosis difficult. The patient developed deep vein thrombosis 2 weeks after the intracranial event and the diagnosis of cortical vein thrombosis was made at that time on MRI study after the resolution of the haemorrhage. This patient actually developed generalized thrombosis as a complication to OHSS. Although the initial MRI picture may be misleading, the diagnosis of thrombosis should always be kept in mind, as it is the commonest cause of intracranial lesions after OHSS.

Key words: IVF/severe OHSS/vascular thrombosis

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication associated with the use of gonadotrophins for ovarian stimulation in an IVF and embryo transfer programme. The association of thrombo-embolic disease with OHSS is considered to be rare. A recent review of 54 reported cases showed that thrombosis could occur on both the arterial (25%) and venous (75%) side (Aboulghar et al., 1998). The usual sites of thrombosis have been described, including internal jugular, subclavian, axillary and mesenteric vessels. Cerebrovascular thrombosis remains the most serious of all and a fatal case has been reported (Cluroe and Synek, 1995). Most of the reported cases of cerebrovascular thrombosis presented as ischaemic infarct. This paper reports a case of cerebrovascular thrombosis which presented as haemorrhagic lesion on magnetic resonance imaging (MRI) of the brain.

Case report

The patient was a 34 year old woman. She presented to us 3 years ago for primary infertility. She had irregular cycles and cycle length varied between 30 and 60 days. Semen analysis of her husband was normal. She was given clomiphene citrate up to 100 mg per day from days 5–9 of each cycle1Department of Obstetrics and Gynaecology, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China hysteroscopy was performed. Both her Fallopian tubes were normal and patent. She was treated with IVF and embryo transfer.

The patient had her first cycle of IVF-embryo transfer in February 1997. Gonadotrophin-releasing hormone agonist (Buserelin; Hoechst Marion Roussel, Germany) 150 µg four times per day was started on day 21 of the pre-treatment cycle for pituitary down-regulation. Transvaginal ultrasound-guided oocyte retrieval was performed after 9 days of human menopausal gonadotrophin (HMG) (Pergonal; Serono, Geneva, Switzerland). Twenty-two ampoules (75 IU per ampoules) of HMG were used. The oestradiol concentration was 17504 pmol/l on the day of human chorionic gonadotrophin (HCG; Profasi; Serono). Nineteen oocytes were obtained, of which 15 fertilized. Three fresh embryos were replaced. Six embryos were of good quality and were frozen. The patient failed to get pregnant and returned for frozen embryo transfer in June 1997. Three embryos were replaced and she conceived. Unfortunately, she aborted at 12 weeks of gestation. She came back for another cycle of frozen embryo transfer in February 1998. Three frozen-thawed embryos were replaced but she failed to get pregnant.

The patient had her second IVF-embryo cycle in January 1999. The pituitary down-regulation and ovarian stimulation were the same as for the first cycle. Twenty-two ampoules (75 IU per ampoule) were used. Transvaginal ultrasound guided oocyte retrieval was performed after 9 days of HMG. The oestradiol concentration was 20808 pmol/l on the day of HCG. Twenty oocytes were obtained of which 19 fertilized. Two embryos were replaced and nine embryos were frozen. She was given progesterone suppository (Utrogestan; Laboratoires Besins Iscovesco, Paris, France) 200 mg three times per day for luteal support. She complained of progressive abdominal distension 13 days after embryo transfer and was admitted to hospital. Ascites was demonstrated on clinical examination. Haemoglobin was 14.5 g/dl and the haematocrit was 0.422. The serum electrolytes were normal and the albumin was 30 g/l. Clotting profile was normal. Urinary output was 1.5 l/day. She was treated conservatively with i.v. fluid 2 l/day.

The patient developed generalized seizure on the next day. She also complained of mild difficulty in writing and other fine motor function of her right hand before the seizure episode.
Clinically there was no post-ictal neurological deficit. Serum concentrations of electrolytes were normal. MRI of the brain showed an abnormal area, about $3 \times 2$ cm, over the left high frontal lobe just anterior to the left precentral gyrus. The lesion was predominantly bright on both T1-weighted and T2 weighted images with evidence of mild vasogenic oedema in the surrounding white matter (Figure 1a). The features were in keeping with a small subacute haematoma. The nature of this lesion was unknown but the provisional diagnosis was a cavernous angioma with haemorrhage. The neurosurgeon was consulted. Since there was no evidence of continuous bleeding and the lesion exhibited no significant mass effect, it was decided to observe the patient and to repeat the MRI of the brain in 4 weeks time to monitor the progress of the lesion. She was given carbamazepine 200 mg twice daily to prevent further seizure. Carbamazepine was used since there was a possibility that she could be pregnant.

The pregnancy test was positive 16 days after embryo transfer. Her abdominal distension became more severe. The haematocrit increased to 0.451 and urinary output decreased to 1 l/day. She also complained of difficulty in breathing. Paracentesis was performed and 2.7 l of ascitic fluid was drained. The symptoms improved and the urinary output increased to 2 l/day. She was discharged from the hospital. Two weeks later, ultrasonography of the pelvis showed a single live intrauterine pregnancy with a crown rump length 5 mm corresponding to 6 weeks gestation.

One week later, the patient complained of left hip pain for 1 week. The left calf was mildly oedematous. There was no dilated superficial vein. Doppler study of the lower limb showed a hypo-echoic thrombus in the left common femoral vein extending into the left external iliac vein. There was no flow signal from these vessels, indicative of acute complete thrombosis. Computerized tomography of the abdomen revealed extensive venous thrombosis up to infrarenal portion of the inferior vena cava (IVC) (Figure 2). Partial thrombosis of the right common iliac vein was also detected (Figure 3). The diagnosis of deep vein thrombosis of lower limbs with extension to the lower IVC was made. In view of the recent history of intracranial bleeding, further assessment of the intracerebral haemorrhage was performed before starting heparin. A repeat MRI of the brain (Figure 4) showed decreased flow void and increased T1 signals in a cortical vein which corresponded to the previously noted subacute haematoma at the left high frontal lobe. The finding suggested cortical vein

Figure 1. T1-weighted images of the left frontal region of the brain showing: (a) the hyperintense haematoma with rim of vasogenic oedema during acute presentation (# marked the hand-motor area of left precentral gyrus) and (b) almost complete resolution of the haematoma 6 months later.

Figure 2. A well-defined intraluminal thrombus inside the inferior vena cava was seen in this post-contrast axial computerized tomography image of the abdomen.

Figure 3. Complete left and partial right common femoral venous thrombosis is shown in this post-contrast axial computerized tomography image of the groin.
Misinterpretation of cortical vein thrombosis in OHSS

OHSS. Cerebrovascular thrombosis is perhaps the most serious of all. Permanent neurological deficit and death have been reported (Rizk et al., 1990; Cluroe and Synk, 1995).

Most of the reported cases of intracerebral thrombosis presented as ischaemic lesions. Both venous and arterial thrombosis have been reported (Stewart et al., 1997). The exact pathogenesis of thrombo-embolism in OHSS is not completely understood. Hypercoagulation state and haemococoncentration have been suggested as the predisposing factors. It is thought that the hypercoagulation status might be due to activation of the plasma kinin system in OHSS (Kodama et al., 1995). A disruption in the coagulation and thrombolysis may explain the hypercoagulable status in OHSS (Aune et al., 1991). In the same investigation, a significant increase in fibrinogen was found and a reduction in antithrombin III concentration in OHSS. Haemococoncentration was proposed as a cause for thrombosis. However, deep cerebrovascular thrombosis has been reported in a patient with moderate ovarian hyperstimulation in whom the haematocrit was not raised (Aboulghar et al., 1998). This raised the concern that some women are genetically predisposed to thrombosis.

Thrombo-embolism with resultant venous infarct and haemorrhagic change. Intracranial angiogram, which showed normal findings, was also performed to rule out any arteriovenous malformation and aneurysm that might contraindicate the use of anticoagulant.

At this time, the patient requested termination of pregnancy. She was very worried about the effect of pregnancy on the intracranial thrombosis and deep vein thrombosis of the lower limb. She was also concerned about the effects of the various drugs on the fetus. After considerable discussion, vacuum aspiration of the uterus was performed at 7 weeks of gestation with no complication. Intravenous heparin was started. After 2 weeks, the heparin was stopped and she was given oral warfarin which was maintained for 6 months. Screening for antithrombin III, Leiden V factor, protein C and S deficiency were negative. There was no neurological deficit and further attack of convulsion. Follow-up MRI studies demonstrated complete resolution of the intracranial haemorrhage (Figure 1b).

Discussion

OHSS is a serious and life-threatening complication. The incidence of significant OHSS complicating assisted reproduction technology is quoted as 0.6-14% (Rizk, 1995). The pathogenesis of OHSS is not well understood. Various strategies for preventing OHSS and its severity have been suggested (Grudzinskas and Egbase, 1998). Progesterone was used for luteal support instead of HCG in this patient in order to avoid OHSS. Perhaps the amount of gonadotrophin for ovarian stimulation could also have been reduced in the second cycle to prevent OHSS in view of the response in the first cycle. However, severe OHSS still cannot be completely eliminated. Thrombo-embolism is the most dangerous complication of OHSS. Cerebrovascular thrombosis is perhaps the most serious of all. Permanent neurological deficit and death have been reported (Rizk et al., 1990; Cluroe and Synk, 1995).

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Anticoagulation therapy is the usual recommended treatment in thrombo-embolism complicating OHSS. In this patient, the initial diagnosis of intracranial thrombosis was not made because MRI showed a haemorrhagic lesion instead of an ischaemic lesion, as commonly reported in the literature. The initial diagnosis was some co-existing lesion in the brain that caused secondary intracranial bleeding. The patient was initially managed conservatively, as there was no neurological deficit. The use of anticoagulation therapy is contraindicated even if the diagnosis of cortical vein thrombosis is known at first presentation because of the risk of inducing further bleeding. She developed deep vein thrombosis of the lower limbs subsequently. Anticoagulation therapy was indicated to prevent pulmonary embolism. The history of recent intracranial haemorrhage made the use of anticoagulant relatively contraindicated. MRI was repeated and the diagnosis of cortical vein thrombosis was revealed. The haemorrhagic change that is not uncommon in venous infarct masked the underlying pathology.

Thus, a single pathogenesis of veno-occlusive disease explained both the intracranial lesion and the deep vein thrombosis. Anticoagulation was started after balancing the risk of further intracranial bleeding and pulmonary embolism. This was a joint decision between the haematologist and the neurosurgeon.

This case illustrates that thrombo-embolism in OHSS is a systemic and generalized phenomenon. The hypercoagulable state can last for several weeks after the onset of OHSS especially if the patient is pregnant. Anticoagulation therapy is the treatment of choice. In cases when anticoagulant is contraindicated, adequate hydration is required. The possibility of deep vein thrombosis should also be monitored. Graduated compression stockings can be used to prevent thrombosis in the lower limbs.
References

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