CASE REPORT

Aorto-subclavian thromboembolism: a rare complication associated with moderate ovarian hyperstimulation syndrome

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The case of an arterial aorto-subclavian thromboembolism associated with a moderate ovarian hyperstimulation syndrome (OHSS) and following ovulation induction for in-vitro fertilization in a young woman is reported. Because of the lack of response to systemic thrombolysis, a left posterolateral thoracotomy was performed on day 8 after embryo transfer. A fibrinocruoric embolus situated at the junction of the left subclavian artery from the aorta was removed through a left subclavian arteriotomy. The distal axillary embolus was removed by a retrograde balloon catheter embolectomy. A moderate OHSS was observed. The ovarian stimulation and OHSS-related risks of thromboembolism are discussed. We conclude that, in the absence of risk factors, counselling about possible complications resulting from stimulation must be emphasized.

Key words: arterial thromboembolism/IVF/menotrophin/ovarian hyperstimulation syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most frequent and worrying complication following ovulation induction. The incidence of this side-effect has increased since gonadotrophin releasing hormone analogues (GnRHα) have been used. For many authors, the different protocols which associate follicle stimulating hormone (FSH) and/or human menopausal gonadotrophin (HMG) with GnRHα seem to be related to a significantly higher rate of moderate or severe OHSS (Rizk and Smitz, 1992). Some authors (Rabau et al., 1967) have classified ovarian response in three clinical categories (mild, moderate and severe) and six grades (two per category) based on the severity of the signs, symptoms and laboratory findings. The more recent definition of OHSS proposed by Golan et al. (1989) has offered a more clinical approach to this syndrome. Severe complications of this iatrogenic syndrome include thromboembolism, adult respiratory distress syndrome, acute hydrothorax (Daniel et al., 1995) and, occasionally, death (Schenker and Ezra, 1994). During ovarian stimulation for in-vitro fertilization (IVF) and embryo transfer, the risk of moderate or severe OHSS after GnRHα/HMG stimulation is evaluated as 0.6–14.0% (Rizk and Smitz, 1992). We report the case of an arterial aorto-subclavian thromboembolism associated with a moderate OHSS in a young woman.

Case report

A non-Caucasian 32 year old woman was treated in our IVF and embryo transfer programme for a secondary infertility associated with a male factor and a bilateral tubal obstruction. Her past medical history reported a right salpingectomy for an ectopic pregnancy and a proximal left tubal occlusion. A mild essential hypertension was easily corrected with labetalol (200 mg/day).

The treatment procedure consisted of a long protocol (Figure 1). After pituitary desensitization with GnRHa (0.1 mg Decapeptyl; Ferring, Zürich, Switzerland) administered from day 23, multiple follicular development was induced using 225 IU HMG (Pergonal; Serono, Aubonne, Switzerland) daily. Follicular growth was monitored with serial ultrasound scans and repeated estimations of oestradiol blood concentrations. On day 10 of stimulation, the HMG dose was reduced to 150 IU because of the high oestradiol concentration (10.5 nmol/l). By day 12, 11 follicles >16 mm in diameter and 16 smaller follicles were observed. The oestradiol concentration reached 17.8 nmol/l when 10 000 IU human chorionic gonadotrophin (HCG; Profasi; Serono) were administered. Oocyte recovery took place 36 h later. In all, 18 oocytes were collected; 12 oocytes fertilized, three embryos were transferred to the uterus 2 days later and nine embryos were frozen. A dose of 1000 IU HCG was given i.m. on the day of embryo transfer and 48 h later for luteal phase support. This support was stopped because the patient complained of nausea and abdominal tension. No diarrhoea or vomiting was noticed. Abdominal ultrasonography showed enlarged ovaries (9 cm).

As expected, multiple ovarian cysts and a small quantity of ascites were found. The haemoglobin concentration was 139 g/l, with a haematocrit of 0.44. Electrolytes and creatinine concentrations were within the normal range. A diagnosis of moderate OHSS was made, based on clinical, laboratory and echographic findings. On day 6 after transfer, the patient began to complain of pain and paraesthesia in the left arm which she had noticed 36 h earlier. Examination revealed pulseless radial and humeral arteries and a cold left arm. The aetiology of the acute ischaemia was determined by an arteriography, which showed a large clot in the left subclavian artery (Figure 2)
and an occlusion of the left axillary artery. Signs of slight haemoconcentration were present (haemoglobin 151 g/l, haematocrit 0.46). Clotting function tests were within the normal range [quick time (PT), partial thrombin time (PTT)]. As thrombolysis was initiated as an emergency procedure, more specific thrombosis risk factors such as protein C, protein S, Leiden V factor and antithrombin III deficiencies were not checked. Immediate local thrombolysis was attempted with 100 000 and 200 000 IU urokinase without success. Anticoagulation using i.v. heparin and oral aspirin was initiated. Given the lack of response, a left postero-lateral thoracotomy was performed on day 7 after transfer. Surgical exploration revealed a fibrinocruoric embolus situated at the junction of the left subclavian artery with the aorta. The embolus was removed through a left subclavian arteriotomy. The distal axillary embolus was removed by a retrograde balloon catheter embolectomy. The presence of a patent foramen oval (paradoxical emboli) was excluded during the operation by using a transoesophageal echocardiography with microbubbles test. The choice of this surgical strategy was motivated by the danger of left carotid arterial emboli after the use of retrograde balloon catheter embolectomy from the left humeral artery. At the end of the operation, the left radial artery was again palpable. Heparin administration was discontinued and dicoumarol administration introduced after the existence of a pregnancy had been excluded.

Discussion
Arterial thromboembolism is a rare complication of OHSS. Only 11 cases of arterial thrombosis have been described following gonadotrophin stimulation: two cases of right middle cerebral artery thrombosis (Neau et al., 1989; Rizk et al., 1990), one of cerebral anterior artery thrombosis (Dumont et al., 1980), one of vertebral artery thrombosis (Humbert et al., 1973), three of internal carotid artery thrombosis (Mozes et al., 1965; Kermode et al., 1993; Aurousseau et al., 1995), one of humeral artery thrombosis (Aurousseau et al., 1995), one of unilateral femoral artery thrombosis (Mozes et al., 1965), one of bilateral femoral artery thrombosis (Choktanisiri and Rojanasakul, 1995) and one of popliteal artery thrombosis (Aurousseau et al., 1995). Most of these occlusions are characterized by their position in the superior limb or in the cerebral territory. The case reported here shows an unusual location of thrombosis occurring during a moderate OHSS.

No risk factor for thromboembolism had been detected, either by clinical observation or by cardiological and laboratory investigations performed before the treatment. Three OHSS risk factors were present: a high oestradiol concentration induced by the simultaneous administration of GnRHα with HMG, ovulation induction with HCG and the use of HCG as a luteal phase support. Only one of the previously described cases of arterial thrombosis presents all these risk factors (Table I).

In our reported case, OHSS risk was, in our opinion, not sufficient to cancel HCG administration or to avoid embryo transfer. In our practice, the cycle is cancelled when the oestradiol concentration is >20 nmol/l or when the number of follicles >16 mm in diameter is >12. This attitude is supported by Morris et al. (1995). Our patient did not develop severe OHSS, although the retrospectively calculated prediction rate according to Delvigne et al. (1993) was 78.9%.

Many factors contribute to thrombogenesis during the evolu-
Table 1. Menotrophins and gonadotrophin-releasing hormone analogue (GnRHa) use in the 11 reviewed cases of arterial thrombosis associated with ovarian hyperstimulation syndrome

<table>
<thead>
<tr>
<th>References</th>
<th>Thrombosis location</th>
<th>HMG</th>
<th>GnRHa</th>
<th>HCG</th>
<th>Ovulation induction</th>
<th>Luteal support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rizk et al. (1990)</td>
<td>Middle cerebral artery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Kermode et al. (1993)</td>
<td>Internal carotid artery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Mozes et al. (1965)</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mozes et al. (1965)</td>
<td>Unilateral femoral artery</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Aurousseau et al. (1995)</td>
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<tr>
<td>Aurousseau et al. (1995)</td>
<td>Humeral artery</td>
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<td>Popliteal artery</td>
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<td>ND</td>
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<td>Dumont et al. (1980)</td>
<td>Cerebral anterior artery</td>
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<td>Neau et al. (1989)</td>
<td>Middle cerebral artery</td>
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<td>No</td>
<td>Yes</td>
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<tr>
<td>Humbert et al. (1973)</td>
<td>Venebral artery</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Choktanasiri and Rojanasakul (1995)</td>
<td>Bilateral femoral artery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

HCG = human chorionic gonadotrophin; HMG = human menopausal gonadotrophin; ND = not described.

The extrinsic coagulation pathway is triggered by endothelial cell procoagulant activity. This activity is involved in thrombogenesis associated with OHSS and seems to be independent of oestradiol and progesterone plasma concentrations.

Independent of the endothelium–blood interface, humoral modifications of haemostasis factors are associated with high plasma concentrations of oestradiol. When the coagulation cascade is triggered, an oestrogen-induced hypercoagulable state is generated by increased activities of several factors (factor VIII, von Willebrand factor and fibrinogen) and by decreased activities of antithrombin III and protein C (Massafera et al., 1993). The decreased activity of factor VII may be interpreted as a relative protective mechanism operating at very high plasma concentrations of oestradiol (Bremme et al., 1994). Currently used laboratory tests such as Quick time, accelerated partial thrombin time, fibrinogen or platelet count have all failed to identify a hypercoagulable state. Whole blood clotting time and whole blood clot lysis time, as used by Aune et al. (1993), are not available for routine investigation. In-vitro clot-based methods, testing the visco-elastic properties of the thrombus, are sensitive methods which are used to investigate the blood hypercoagulability associated with ovarian stimulation. However, they have failed to describe the platelet and vascular endothelium interface.

In conclusion, whether thrombogenesis is dependent upon important hormonal changes induced by stimulation, vascular damage, haemostasis modifications or all these factors is not clear.

Conclusion

In our reported case, arterial thrombosis occurred even though a moderate OHSS was present. Although a moderate OHSS was predictable, the risk of arterial thrombosis was not. This emphasizes the importance of informing patients about possible complications associated with stimulation.

References


Delvigne, A., Dubois, M., Bauneh, B. et al. (1993) The ovarian hyperstimulation syndrome in in-vitro fertilization: Belgian multicentric
M.Germond et al.


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