CASE REPORT

Internal jugular vein thrombosis caused by resistance to activated protein C as a complication of ovarian hyperstimulation after in-vitro fertilization

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We present a case of a 24 year old woman who became pregnant (twins) after human menopausal gonadotrophin (HMG)-induced ovarian stimulation, in-vitro fertilization (IVF) and subsequent embryo transfer. She developed a right internal jugular vein thrombosis as a complication of severe ovarian hyperstimulation syndrome (OHSS) 28 days after embryo transfer. The thrombosis developed in spite of anticoagulation with low-dose heparin. Later a resistance to activated protein C (APC) or Dahlbäck disease was diagnosed. Due to a new test procedure (accelerin inactivation test), the diagnosis was possible even under anticoagulation treatment. The coincidence of hyperstimulation and internal jugular vein thrombosis with the concurrent diagnosis of resistance to APC has not been published previously. The benefit of general screening for resistance to APC before admission to the IVF programme should be weighed. Targeted selection of a group of high-risk women would therefore be made possible.

Key words: internal jugular vein thrombosis/in-vitro fertilization/ovarian hyperstimulation syndrome/resistance to APC

Introduction

In spite of advances in observation techniques, ovarian hyperstimulation syndrome (OHSS) remains one of the most frequently reported complications of human menopausal gonadotrophin (HMG)-induced ovarian stimulation of infertile women. Clinically stimulation is monitored primarily via ultrasound (McArdle et al., 1983) and oestradiol concentrations. The literature describes a large variation in the severity of OHSS following HMG-stimulation (Engel et al., 1978; Schenker and Weinstein, 1978; Navot et al., 1988; Delvigne et al., 1991), whereby the authors report a frequency of 0.1–5% for the severe form. Mild to moderate cases do not usually have clinical consequences. Severe OHSS must be regarded as a potentially lethal complication requiring immediate therapy as well as close patient monitoring. The pathophysiology of OHSS is poorly understood. An increased risk is associated with high oestradiol levels, young age, a large number of small follicles (Navot et al., 1988) and polycystic ovaries (PCO) (MacDougall et al., 1993). The disease is further associated with changes in the renin–angiotensin system and prostaglandin metabolism (PG12) (Navot et al., 1987; Ong et al., 1991; Phillips et al., 1995). Elevated plasma levels of von-Willebrand–Jürgens factor are observed (Todorow et al., 1993) as well as other changes in coagulability and fibrinolytic activity (Phillips et al., 1995). A particularly severe complication of OHSS is thromboembolism, for which Delvigne et al. (1993) reported a prevalence of one out of 128.

The following case describes a patient who became pregnant (twins) after in-vitro fertilization (IVF) and subsequent embryo transfer. She developed a right internal jugular vein thrombosis as a complication of severe OHSS. The thrombosis developed in spite of anticoagulation with low dose heparin. A thrombophilic dysaccelerinemia, more commonly known as thrombophilic disorder, and also described as resistance to activated protein C (APC) or Dahlbäck disease (Dahlbäck and Hildebrand, 1994) was later diagnosed in the patient.

Case report

IVF and subsequent embryo transfer were accomplished in a 24 year old nulligravida woman. Her partner suffered from severe oligoasthenoteratozoospermia. Ovarian stimulation was initiated with triptorelin acetate, followed by administration of HMG for 14 days. Under this protocol the oestradiol concentration rose from 5.47 pmol/l on day 1 of HMG administration to 27 312 pmol/l on day 13 of HMG administration.

The sonographically controlled aspiration of 20 oocytes proceeded without complication. Three embryos were transferred. The first positive human chorionic gonadotrophin (HCG) value (125 IU/l) was found 2 weeks later. After ambulant care the patient was admitted to hospital because of progressive symptoms of hyperstimulation 4 weeks following embryo transfer. The examination indicated massive ovarian enlargement (multiple ovarian cysts with a diameter up to 6 cm) and also a massive fluid accumulation in the peritoneal cavity. In the course of the normal therapeutic regime (infusion treatment, albumin substitution, anticoagulation with 2×5000 I.U. s.c. heparin/day), an initial worsening of symptoms occurred with increasing HCG concentrations, so that (17 days post-embryo transfer) an ascites puncture was necessary. After the symptoms had slightly improved 11 days later, the haematocrits were normal and the HCG values rose to 13.528 mIU/ml, the patient complained of right neck pain. The initial physical examination identified occluded right neck veins.

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Thrombosis and OHSS

Table I. Clinical and laboratory parameters of the patient presented

<table>
<thead>
<tr>
<th>Date (1995)</th>
<th>9 April</th>
<th>23 April</th>
<th>4 May</th>
<th>22 May</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days post embryo transfer</td>
<td>3</td>
<td>17</td>
<td>28</td>
<td>46</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52</td>
<td>58</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Left ovary dimensions (mm×mm)*</td>
<td>80×70</td>
<td>90×70</td>
<td>90×70</td>
<td>70×50</td>
</tr>
<tr>
<td>Right ovary dimensions (mm×mm)*</td>
<td>90×70</td>
<td>80×60</td>
<td>90×70</td>
<td>60×50</td>
</tr>
<tr>
<td>Ascites*</td>
<td>large</td>
<td>excessive</td>
<td>excessive</td>
<td>moderate</td>
</tr>
<tr>
<td>Haematocrit (37-47%)</td>
<td>46.7</td>
<td>38.0</td>
<td>39.2</td>
<td>31.4</td>
</tr>
<tr>
<td>White blood cell count/μl (4000-11 000)</td>
<td>14.9</td>
<td>11.0</td>
<td>9.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Platelets/μl (15 000-40 000)</td>
<td>343 000</td>
<td>489 000</td>
<td>387 000</td>
<td>389 000</td>
</tr>
<tr>
<td>aPTT (25-40)</td>
<td>27.9</td>
<td>23.3</td>
<td>61.5*</td>
<td>31.5</td>
</tr>
<tr>
<td>Na+ mmol/l (135-145)</td>
<td>133</td>
<td>128</td>
<td>130</td>
<td>132</td>
</tr>
<tr>
<td>K+ mmol/l (3.5-5.0)</td>
<td>4.0</td>
<td>3.7</td>
<td>4.3</td>
<td>4.4</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time (s).
*Transvaginal ultrasound studies.
1Date of admission, start of anticoagulation with 2×5000 I.U. s.c. heparin/day.
2Date of vein thrombosis, start of anticoagulation with 2×5000 I.U. i.v. heparin/day.
3Under high dose of heparin (25 000 I.U. i.v. heparin/24 h).
4Date of demission.

Otherwise, the only complaints were associated with the ovarian hyperstimulation. The suspicion of a right internal jugular vein thrombosis was confirmed by colour-Doppler-ultrasound and presented itself extended to the upper pole of the thyroid gland. The subclavian vein remained free while the right jugular vein showed compensatory enlargement. That same day, abdominal and vaginal ultrasound showed no change in either ascites or the condition of the ovaries compared to the initial examination. Two gestational sacs were found, but no embryonic structures could be seen. Laboratory analysis indicated a decreased haematocrit of 0.38 and thrombocytosis of 489 000 platelets/μl (Table I); the protein concentrations were normal. Tests of haemostasis under low-dose heparinization (2×5000 I.U. s.c. heparin/day) were in the normal range. After the internal jugular vein thrombosis was conclusively diagnosed, continuous high-dose anticoagulation (25 000 I.U. i.v. heparin/24 h) was initiated and controlled daily by the activated thromboplastin time (aPTT) (Table I). After 9 days of high-dose heparinization, vaginal bleeding was observed. Vaginal sonography showed two gestational sacs with vital embryos. In one of the gestational sacs a haematoma with a diameter of 1.5 cm was documented. Therefore, the heparin dose was again reduced to 2×7500 I.U. s.c./day. Doppler sonographic investigation of the internal jugular vein thrombosis demonstrated increasing organization but no enlargement. Ascites as well as cystic remodelling of the ovaries were still apparent, but receding at the time of release (48 days after embryo transfer). Neither the patient's nor the family's medical histories indicated venous thromboembolisms. Plasma concentrations of antithrombin III, fibrinogen, factor XII, C1-inhibitor, protein C, protein S, and α-2-antiplasmin were within the normal range as were anticardiolipin–immunoglobulin (Ig)G and IgM. Values for resistance to APC, accelerin-inactivation and protein S-antigen were all clearly below the lower reference values. Molecular analysis using the polymerase chain reaction (PCR) technique (Bertina et al., 1994) verified that the patient had the heterozygotic (G1691) mutation for factor-V.

The patient subsequently felt well. We continued the heparinization (2×7500 I.U. s.c. heparin/day) and the hyperstimulation symptoms have steadily subsided. After treatment of preterm labour for 8 weeks, the pregnancy was determined in the 36th gestational week by a Caesarian section. The children were healthy and weighed 2400 and 2500 g.

Discussion

Severe OHSS is a complication associated with HMG-induced ovulation. Furthermore, anticoagulation treatment rarely brings about vascular thrombosis. Worldwide, only eight cases around the head and neck region have been described, the first being Mozes et al. (1965), who reported a fatal left internal carotid artery thrombosis following HMG-stimulation. Rizk et al. (1990), described a patient whose right arteria-cerebri media closed after explorative laparotomy. Mills et al. (1992), reported two cases of subclavian vein thrombosis as late complications of OHSS. Only four papers, Fournet et al. (1991), Ong et al. (1991), Bachmeier et al. (1994) and Benifia et al. (1994), described an internal jugular vein thrombosis associated with severe hyperstimulation. In all eight reports, the coagulation screening showed no indications of primary pathological haemostasis.

The coincidence of hyperstimulation and internal jugular vein thrombosis with the concurrent diagnosis of a thrombophilic dysaccelerinaemia (resistance to APC, Dahlbäck disease) has not been published previously. Bertina et al. (1994) have shown that a specific point mutation (nucleotide position 1691) in the gene coding for coagulation factor-V is responsible for the defect in most patients. This factor-V gene produces a factor-V molecule which cannot be inactivated properly by activated protein C. A 3–5% frequency of this so-called 'factor-V Leiden' was shown in the Dutch population (Koster et al., 1993; Bertina et al., 1994). Thus, the calculated genetic risk of APC-resistance is about 10-fold higher than the risk for antithrombin-III, protein-C, and protein-S deficiencies. The prevalence of the mutation is significantly higher among men who have venous thrombosis, pulmonary embolism, or both (Ridker et al., 1995).
A new test procedure (accelerin inactivation test) allows diagnosis of resistance to APC even during anticoagulation treatment (Hintz et al., 1995). The method is based on a modified activated partial thromboplastin time (aPTT) similar to the standard APC test (Rosen et al., 1994). But by using a 1:20 dilution of the test plasma mixed with factor V-deficient normal plasma, the test is no longer influenced by anticoagulants (due to dilution) or factor deficiencies (due to factor V deficient normal plasma). The normal range is >50%.

Kaaja et al. (1989) reported additional changes in the coagulation system during severe OHSS following HMG stimulation. He showed decreased antithrombin III concentrations during anticoagulation therapy. After the therapy had been interrupted, these parameters returned to their normal values. Phillips et al. (1995) reported increased factor-V, fibrinogen, and profibrinolyisin concentrations as well as shortened partial thromboplastin times in severe OHSS. Considering that the pathological mechanism has not been fully determined, it is doubtful that minor alterations can significantly contribute to the pathogenesis of thrombosis. Additional risk factors for internal jugular vein thrombosis are iatrogenic compression due to the enlarged ovaries and ascites formation, i.v. drug abuse, tumour compression, and even paraneoplastic phenomena (Trussaud syndrome). We could rule out such factors.

Additionally, unspecified risk factors such as increased oestradiol concentrations and hyperstimulation-associated patient immobilization must be considered. Also, mechanical compression due to the enlarged ovaries and ascites formation may contribute to thrombosis, although these might have an effect on deep vein thrombosis of the legs (Rosen et al., 1994).

The discovery of thrombophilic dysaccelerinaemia by Dahlbäck and Hildebrand (1994) as well as the refinement of the pathological model by Bertina et al. (1994), have shown that this condition occurs quite frequently. Only now, with the new functional test, can resistance to APC be detected during anticoagulation treatment (Hintz et al., 1995). Patients who develop venous thrombi during low-dose heparin prophylaxis must be considered as potential candidates for thrombophilic disorders such as APC resistance. This is especially true since the patients undergoing IVF are usually young and otherwise healthy.

The benefit of general screening for resistance to APC before admission to the IVF programme should be weighed. The coincidence of OHSS and resistance to APC brings with it an increased risk of thromboembolic events. Targeted selection of a group of high risk women would therefore be made possible.

References


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