Case report

Aphasia: an early uncommon complication of ovarian stimulation without ovarian hyperstimulation syndrome

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Abstract

Thromboembolic disease associated with assisted reproductive techniques is extremely rare. A 21-year-old woman with primary infertility underwent an ovulation induction cycle with luteal long protocol. Twenty-four hours following oocyte retrieval, the patient complained of difficulty in speaking. On neurological examination, mild disorientation, motor aphasia, and right-sided hypoesthesia were noted. Brain computed tomography scanning without contrast revealed left parietal lob infarct. Brain magnetic resonance imaging (MRI), MRI angiography (MRA) and perfusion MRI demonstrated an occlusion of the posterior division of the left middle cerebral artery (MCA). Physical, ultrasound examinations and laboratory test evaluation failed to reveal ovarian hyperstimulation syndrome. Except for ovarian stimulation, no additional risk factors for stroke were shown. Following anticoagulation and speech therapy, the patient recovered completely within eight months. One year after the left MCA thrombosis, she conceived spontaneously and had an uncomplicated vaginal delivery of a live male infant weighing 2900 g at 38 weeks gestation. This case supports that ovulation induction and assisted reproductive techniques may be a newly recognized cause of cerebral infarction in otherwise healthy women.

Keywords: *aphasia, arterial occlusion, assisted reproduction, ovulation induction, stroke, thrombosis*

Introduction

The incidence of thromboembolic disease associated with assisted reproductive techniques is considered to be extremely rare. From reviews of these techniques, it is often inferred that venous thrombosis is the most likely thromboembolic phenomenon to be encountered. However, only a few of cases with thromboembolic disease following ovarian stimulation have arterial thromboses and most of them are intracerebral and associated with ovarian hyperstimulation syndrome (OHSS) (Ayhan *et al*., 1993; Stewart *et al*., 1997; Rao *et al*., 2005).

The exact aetiology and pathogenesis of this rare condition is unknown. The reasons outlined are reduced venous return secondary to enlarged ovaries, particularly in the case of ovarian hyperstimulation syndrome (OHSS), immobility and ascites, especially for venous thrombosis cases. These anatomical features are compounded by hypercoagulable state induced by high oestrogen concentration and, in OHSS, haemoconcentration and reduced circulating blood volume (Stewart *et al*., 1997).

In this report, a case of motor aphasia resulting from thrombosis in the posterior division of the left middle cerebral artery (MCA) following ovarian stimulation without OHSS, 24 h after oocyte retrieval is reported.

Case report

A 21-year-old woman with a history of 2 years of primary infertility was accepted to the centre for her first intracytoplasmic sperm injection (ICSI) cycle. Her medical and family histories were unremarkable for systemic and familial diseases and thrombophilia. Her partner suffered from severe oligoasthenozoospermia. She underwent an ovulation induction cycle with the long luteal protocol. Leuprolide acetate (1.0 mg Lucrin, Abbott, Turkey) was started at the luteal phase. Recombinant FSH (rFSH, Gonal-F, Serono, Turkey) was administered in a step-down fashion, starting with a 300 IU/day according to the documentation of suppression during menses; and after 5 days the dose was adjusted according to the ovarian response (dose was decreased to 225 IU on day 5, 200 IU on day 6, 150 IU on day 7, 100 IU on days 8–9, 75 IU on days 10–11). Follicular growth was monitored using serial ultrasound scans and serum oestradiol measurement. On day 12 of rFSH administration, with an oestradiol concentration of 2118 pg/ml, four follicles were between 18 and 20 mm and 12 follicles were between 14 and 17 mm diameter. Human chorionic gonadotrophin (HCG, 10,000 IU i.m., Profasi 5000 IU, Serono, Turkey) was administered. Transvaginal oocyte retrieval was scheduled 36 h after HCG injection with the retrieval of 10 oocytes. During oocyte collection, the woman received mild i.v. sedation with propofol (2 mg/kg). Of these oocytes, 10 were metaphase II and were microinjected. Six cleaved embryos were obtained.

Twenty-four hours after oocyte retrieval, the patient complained of difficulty in speaking. At the emergency room, her blood pressure was 130/80 and pulse rate was 98 beats per minute. On neurological examination, mild disorientation, motor aphasia, and right-sided hypoesthesia were noted. The other physical examination findings were unremarkable. Physical, ultrasound examinations and laboratory test evaluation failed to reveal OHSS. However, brain computed tomography without contrast revealed left parietal lobe infarct. With an impression of acute left supratentorial stroke, brain magnetic resonance imaging (MRI), MRI angiography (MRA) and perfusion MRI were performed. Brain MRI showed bright high-signal intensity in the left MCA territory on diffusion-weighted image, suggesting an acute MCA infarct (**Figure 1**). MRA and perfusion MRI demonstrated an occlusion of the posterior division of the left MCA (**Figure 2**).

Complete blood counts showed white blood cell at 9500/l, while haemoglobin (11.9 g/dl) and haematocrit (34.9%) were slightly decreased. Platelet counts were normal (222,000/l). Liver, renal function tests and serum electrolyte concentrations were all within normal limits. The coagulation profile showed that the patient's prothrombin and activated partial thromboplastin time were both in normal ranges. Transthoracic echocardiography did not find any cardiac abnormalities. Despite a negative family history, to exclude evidence of the most common causes of thrombophilia activated protein C resistance, prothrombin 20210A mutation, antiphospholipid (anticardiolipin or beta-2-glycoprotein I) antibodies, plasma homocysteine, protein C,

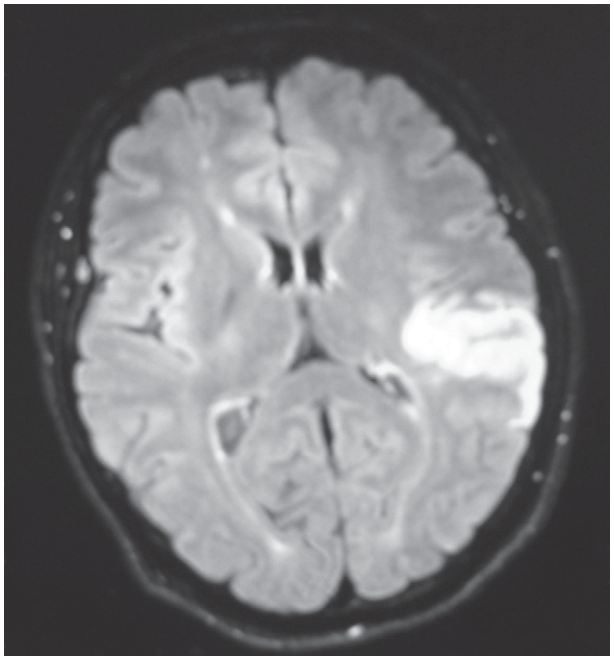

Figure 1. Axial T2 – weighted magnetic resonance image showing the acute left middle cerebral artery infarct.

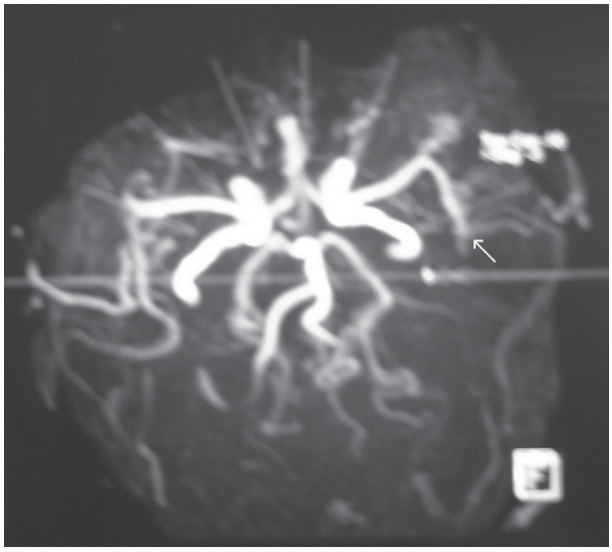

Figure 2. Brain magnetic resonance angiography demonstrating occlusion in the posterior division of left middle cerebral artery (arrow).

protein S, antithrombin III deficiencies and factor V Leiden mutation were assayed and no abnormalities were found. Furthermore, the detailed physical examination also failed to reveal any findings of Behçet's disease. In addition, both lupus anticoagulant and autoimmune screen (anti-dsDNA, ANA) were unremarkable.

Following the diagnosis of acute cerebral stroke, the embryos were frozen and anticoagulation using i.v. heparin and oral aspirin were initiated. The patient made a dramatic improvement in her neurological condition over the following 72 h and continued to improve gradually thereafter. A week later, she was discharged from the hospital on aspirin once daily (75 mg) with oral warfarin therapy. Speech therapy was commenced. The patient recovered completely within eight months. One year after the left MCA thrombosis, she conceived spontaneously and had an uncomplicated vaginal delivery of a live male infant weighing 2900 g at 38 weeks gestation.

Discussion

The possible risk factors for thrombosis are increased age, obesity, a past history of thromboembolism, varicose veins, use of the oral contraceptive pill, malignancy, factor V Leiden gene mutation, general anaesthesia and orthopedic surgery, hormone replacement therapy, gender, ethnicity or race, chemotherapy, other thrombophilias, cardiovascular factors, smoking and blood type (Edmonds *et al*., 2004). Furthermore, inherited thrombophilias are also associated with implantation failure, which may be related to microvascular thrombosis (Coulam *et al*., 2006). However, the existing literature regarding ovulation induction and risk of thrombosis is scant and confined to case reports, and definite conclusions about the risk of thrombosis cannot be drawn (Yinon *et al*., 2006).

OHSS and thromboembolic disease are the most serious of the complications following ovulation induction. Furthermore, a thromboembolic phenomenon is an extremely rare complication and the majority of thromboses reported have been at venous sites. Only a few cases of arterial thrombosis have been described following gonadotrophin stimulation and also only a few of them have been intracerebral (Inbar *et al*., 1994; Hwang *et al*., 1998; Yoshii *et al*., 1999).

Stroke following gonadotrophin stimulation for assisted reproduction is almost always associated with OHSS. It is thought that the extreme haemoconcentration, hyperviscosity, stasis and an associated thrombophilic disorder predispose to thrombosis, but increased coagulation factors and platelets also have roles in OHSS-associated thrombosis (Davies and Patel, 1999; Koo *et al*., 2002). However a case of stroke has been documented in a patient on gonadotrophin therapy but without any clinical evidence of OHSS (Inbar *et al*., 1994). Higher ovarian hormone concentrations associated with assisted reproduction protocols may trigger the coagulation cascade towards thrombus formation. This case had cerebral infarct following ovarian stimulation with rFSH for ICSI but without any clinical and laboratory evidence of OHSS.

The time between the day of administration of HCG and acute cerebral infarct has been reported to range from five to 36 days (Stewart *et al*., 1997). In this case, the early occurrence of MCA occlusion may suggest the possible effect of rFSH on thrombosis in the absence of other contributing risk factors. However, it is possible that this case of cerebral infarction may have occurred coincidentally or in a background not thoroughly investigated and may not be clearly assigned as a 'formal complication' of ovarian stimulation: certainly it seems to be an extremely rare association.

Although there were no risk factors for thrombosis in the current case, it was suggested in a recent study that during ovulation induction in patients at risk for thrombosis, the introduction of low molecular weight heparin (LMWH) as a cycle-protective treatment was not associated with any medical complication. The use of a controlled spontaneous cycle with LMWH is suggested in very-high-risk patients (Yinon *et al*., 2006).

In this reported case, cerebral arterial thrombosis occurred even in the absence of clinical and laboratory manifestations of OHSS. Although the risk of stroke following ovarian stimulation was not predictable in the absence of possible predisposing factors, clinicians should be aware of this rare complication. In addition, when a patient complains of difficulty in speaking, the rare complication of acute cerebral infarct should be kept in mind. This report also emphasizes the importance of informing patients about possible arterial thrombotic complications associated with ovarian stimulation.

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