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Common carotid artery thrombosis and malignant middle cerebral artery infarction following ovarian hyperstimulation syndrome: A case report

Xu YT *et al.* Carotid artery thrombosis with OHSS

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Abstract

BACKGROUND

Arterial thrombosis is a serious and rare complication of ovarian hyperstimulation syndrome (OHSS). Herein, we described a case of OHSS complicated with common carotid artery thrombosis and malignant middle cerebral artery infarction after egg retrieval and before embryo transfer.

CASE SUMMARY

¹² A 32-year-old female with family history of thrombosis and undergoing *in vitro* fertilization due to unexplained infertility, was admitted due to abdominal distension for 3 d and coma for 2 h. She received egg retrieval 7 d ago and embryo transfer was not performed yet. Blood biochemical analysis showed estrogen of 15781 pmol/L. Gynecological examination showed palpable masses on both sides of the adnexal areas. Ultrasound observed enlarged ovaries and abdominal ascites. Imaging examination of head and neck revealed fresh malignant middle cerebral artery infarction in the left side of brain and internal carotid artery as well as occlusion in the left ¹ carotid artery, internal carotid artery, and ² middle cerebral artery. Finally, the case was diagnosed as severe OHSS, complicated by common ² carotid artery thrombosis and malignant middle cerebral artery infarction. Liquid replacement, anticoagulation, vascular endothelium protection, brain protection and decompressive craniectomy were administrated. Then, rehabilitation training was performed for 6 mo. At present, she had poor speaking ability and decreased muscle strength on the right side.

CONCLUSION

There is risk of thrombosis in any period of OHSS. During *in vitro* assisted reproduction, for cases with a family history of thrombosis, hyperlipidemia and other high-risk factors, serum lipid levels should be controlled as soon as possible to improve metabolic dysfunction. Once thrombosis is formed, timely and effective treatments should be performed to improve the prognosis.

Key Words: Ovarian Hyperstimulation Syndrome; Arterial Thrombosis; Cerebral Infarction; Thrombophilia; Case report

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Core Tip: Arterial thrombosis is a serious and rare complication of ovarian hyperstimulation syndrome (OHSS), which can be life-threatening without timely treatments. Herein, we reported a case of OHSS complicated with common carotid artery thrombosis and malignant middle cerebral artery infarction after egg retrieval and before embryo transfer. Based on the characteristics of this case, we conclude that thrombosis may occur in any period of OHSS. During *in vitro* assisted reproduction, for cases with high risk factors for thrombosis (such as hyperlipidemia), metabolic dysfunction should be corrected. Once there is thrombosis, timely and effective treatments should be performed to improve the prognosis.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS), a rare and unique complication associated with *in vitro* assisted reproduction, is an excessive response to exogenous gonadotropins, which is characterized by multiple follicles in bilateral ovaries, enlarged ovaries,

abnormal capillary permeability, and abnormal extravasation of body fluids and proteins. It is diagnosed based on symptoms (such as abdominal distension), physical examination (such as enlarged ovaries), imaging examination (such as ascites), and laboratory examination (such as coagulation abnormalities and hormone levels). According to Golan's classification^[1], it is divided into mild (grade 1 and 2), moderate (grade 3) and severe OHSS (grade 4 and 5). Severe OHSS may cause renal failure, hypovolemic shock, thromboembolism, respiratory distress syndrome, and even death. Thrombosis is a serious complication of OHSS with an incidence rate of 0.11%^[2]. Arterial thrombosis as a complication of OHSS is extremely rare, which can be life-threatening without timely treatments. In this report, we introduced a case of OHSS complicated with common carotid artery thrombosis and malignant middle cerebral artery infarction after egg retrieval and before embryo transfer.

CASE PRESENTATION

Chief complaints

OHSS, a rare and unique complication associated with *in vitro* assisted reproduction, is an excessive response to exogenous gonadotropins, which is characterized by multiple follicles in bilateral ovaries, enlarged ovaries, abnormal capillary permeability, and abnormal extravasation of body fluids and proteins. It is diagnosed based on symptoms (such as abdominal distension), physical examination (such as enlarged ovaries), imaging examination (such as ascites), and laboratory examination (such as coagulation abnormalities and hormone levels). According to Golan's classification^[1], it is divided into mild (grade 1 and 2), moderate (grade 3) and severe OHSS (grade 4 and 5). Severe OHSS may cause renal failure, hypovolemic shock, thromboembolism, respiratory distress syndrome, and even death. Thrombosis is a serious complication of OHSS with an incidence rate of 0.11%^[2]. Arterial thrombosis as a complication of OHSS is extremely rare, which can be life-threatening without timely treatments. In this report, we introduced a case of OHSS complicated with common carotid artery thrombosis and

malignant middle cerebral artery infarction after egg retrieval and before embryo transfer.

History of present illness

Abdominal distension started 3 d ago before presentation with coma.

History of past illness

The patient underwent *in vitro* fertilization for unexplained infertility. Egg retrieval was performed 7 d ago but embryo transfer was not performed yet.

Personal and family history

The patient had a family history of thrombosis but denied the history of polycystic ovary syndrome.

Physical examination

Physical examination showed blood pressure 80/50 mmHg, heart rate 120 beats/min, well-proportioned body, subcoma, obvious abdominal distension, positive shifting dullness, high muscle tone, and Babinski sign (+). National Institutes of Health Stroke Scale (NIHSS) score at admission was 29. Gynecological examination showed that the masses were palpable on both sides of the adnexal areas, with mass size of 9 cm × 7 cm × 7 cm on the left side, and the mass size of 12 cm × 8 cm × 8 cm on the right side.

Laboratory examinations

As show in Table 1, blood tests revealed white blood cell count $29.82 \times 10^9/L$, hematocrit 0.454, platelet count $269 \times 10^9/L$, hemoglobin 151 g/L, fibrinogen content 5.19 g/L, antithrombin III 85.3%, total cholesterol 5.71 mmol/L, triglycerides 2.81 mmol/L, free fatty acids 1.34 mmol/L, low-density lipid cholesterol 3.76 mmol/L, homocysteine 9.4 $\mu\text{mol/L}$, high-density lipid cholesterol 1.05 $\mu\text{mol/L}$, and estrogen 15781 pmol/L.

Imaging examinations

Gynecological color Doppler ultrasound showed that both ovaries were enlarged. The size of the left ovary and right ovary was about 9.0 cm × 6.6 cm and 12.0 cm × 7.9 cm, respectively. Abdominal cavity B-ultrasound showed a lot of ascites with the largest anteroposterior diameter of the dark area of about 6.2 cm. These findings indicated severe OHSS. Head magnetic Resonance Imaging + magnetic resonance angiography (MRA) observed a large area of fresh malignant middle cerebral artery infarction on the left side, suggesting occlusion of the middle cerebral artery (Figure 1) and the left internal carotid artery (Figure 2). On head and neck computed tomography angiography (CTA), the left carotid artery, internal carotid artery, and left middle cerebral artery were occluded, suggesting common carotid artery thrombosis (Figure 3).

FINAL DIAGNOSIS

The final diagnosis was OHSS complicated with common carotid artery thrombosis and malignant middle cerebral artery infarction.

TREATMENT

Fluid replacement, anticoagulation with low molecular weight heparin sodium, vascular endothelium protection with atorvastatin, brain protection with edaravone and butylphthalide, and, intracranial pressure reduction with mannitol and furosemide were administrated. During treatment, decompression with left side craniectomy was performed due to worsened cerebral edema. Symptomatic and rehabilitation treatment were performed following surgery.

OUTCOME AND FOLLOW-UP

At present, the speaking ability of the patient was awkward. She could walk for a few steps with support. The left limb muscle strength was level 5, left muscle tone was normal, and left pathology sign was (-). The right upper limb muscle strength was level 2, right lower limb muscle strength was level 4, right muscle tone was decreased, and

right pathological sign was (+). The discharge NIHSS score was 8. The patient is under constant follow-up.

DISCUSSION

Malignant middle cerebral artery infarction is a devastating type of ischemic stroke. The main clinical factors associated with malignant middle cerebral artery infarction include decreased level of consciousness, nausea or vomiting, and heavy smoking^[3]. The most closely related pathogenesis of carotid artery thrombosis is atherosclerotic plaque. Other mechanisms of carotid artery thrombosis include hypercoagulability, hyperfibrinogenemia, hyperlipidemia, and antiphospholipid syndrome^[3,4]. Digital subtraction angiography is the gold standard for the diagnosis of carotid artery thrombosis^[5], but MRA, CTA or Doppler ultrasound can also be used to confirm carotid artery thrombosis.

The incidence of OHSS complicated by thrombosis is only 0.04%^[6]. Among the thrombosis complicated with OHSS, arterial thrombosis accounts for 19%, which usually occurs at the same time as OHSS, and within 2 wk after embryo transfer (average 10 d). Venous thrombosis related with OHSS accounts for 81%, which usually occurs within 1 wk to 3 mo of pregnancy after embryo transfer, or after the relieve of clinical OHSS symptoms (an average of 40 d to 42 d after embryo transfer), and mostly locates in upper limbs^[7-9].

For the case in this study, she underwent *in vitro* fertilization for unexplained reasons, denied the history of polycystic ovary syndrome, and had thrombosis family history. Abdominal distension occurred during the assisted pregnancy. Hyperlipidemia and shifting dullness were found during physical examination. B-ultrasound indicated ascites and the size of bilateral ovaries increased. The estrogen level increased to 15781 pmol/L, the red blood cell ratio was 0.454, and the white blood cell count was $29.82 \times 10^9/L$, suggesting severe OHSS. Common carotid artery thrombosis was formed after egg retrieval (before embryo transfer), involving in internal carotid, external carotid

and intracranial arteries. The thrombosis had characteristics of wide range and large area, and early than the peak of OHSS.

The main pathological basis of arterial thrombosis is endothelial cell damage in the vascular wall, which is mostly resulted from atherosclerosis and abnormal lipid metabolism, and further induces platelet aggregation and initiates the coagulation and fibrinolysis system^[10]. Hyperlipidemia can cause changes in the composition and function of blood coagulation factors, increase blood viscosity, slow blood flow and local vortex formation, and thereby promote thrombosis^[11,12]. OHSS patients are mostly accompanied by an increase in the number of white blood cells. The activated multinucleated leukocytes and neutrophils that can produce a large amount of reactive oxygen species and cathepsin G, and the increased level of ovarian-derived inflammatory cytokines can cause vascular endothelial cell damage^[13]. The patient in this report developed OHSS during *in vitro* assisted reproduction. The patient was also complicated with hyperlipidemia. OHSS and hyperlipidemia may together result in thrombosis. It has been shown that 47% of patients with arterial thrombosis have a hypercoagulable state^[4]. In this study, the patient had severe OHSS and high levels of estrogen. High levels of estrogen can increase vascular permeability, leading to hemoconcentration, hypovolemia, further activation of vasoactive substances, and, hypercoagulability, which may be the cause of carotid artery thrombosis and non-atherosclerotic plaque. In young adults, cerebral infarction and vascular brain disease can also be caused by hematological disorders^[14]. The patient in this report should receive further tests to exclude thrombosis due to blood diseases, such as factor V Leiden, prothrombin gene mutation, plasma homocysteine, aCL antibody, lupus anticoagulant, anti-2 glycoprotein I antibody, *etc*.

The patient in this report had a family history of venous thromboembolism, suggesting the possibility of inherited thrombophilia. Thrombophilia is a disease state that is prone to thromboembolism due to gene mutations leading to lack of anticoagulant protein or deficiency of coagulation factor and plasminogen^[15]. According to the etiology, it is divided into inherited thrombophilia and acquired thrombophilia. The main clinical feature of thrombophilia is thrombosis proneness. Anticoagulant protein deficiency is the

most common disease in the Chinese population^[16]. The patient of this study displayed the characteristics of inherited thrombophilia. She and her relatives should receive further measurement of antithrombin III activity, protein S activity and protein C activity to evaluate the risk of thrombosis, thus providing valuable evidence for early anticoagulation in assisted reproduction.

CONCLUSION

In summary, in assisted reproduction, OHSS should be actively prevented, and physicians should be highly vigilant that there is a risk of thrombosis in any period of OHSS. For OHSS patients with iatrogenic or non-iatrogenic risk factors of thrombosis, and a family history of thrombosis and hyperlipidemia, early evaluation and control of lipid levels should be performed to minimize the occurrence of thrombosis and improve the prognosis.

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