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Acute Cerebrovascular Accidents Secondary to Internal Carotid Artery Thrombosis in Severe Ovarian Hyperstimulation Syndrome (OHSS)

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Abstract

Severe Ovarian Hyperstimulation Syndrome (OHSS) is an uncommon iatrogenic complication, and complicated cerebral infarctions is exceedingly rare.

We present a case of 39-year-old young woman with left cerebral infarctions due to OHSS in first trimester of pregnancy after ovulation induction therapy. At beginning, she was treated with paracentesis conservatively at same clinic of district hospital. Later on, she was transferred to our medical center due to neurological deterioration from large left hemispheric infarctions with pending uncal herniation, and the craniotomy and lobectomy were performed in our medical center. The pregnancy was terminated at 12 weeks gestation for management of OHSS complicated with cerebral infarctions. Due to left hemispheric infarctions, she had neurological deficits with the functional impairments of right hemiplegia and global aphasia. After 6 weeks of intensive rehabilitation, she was able to ambulate with assistance but could speak only a few words at discharged.

Knowledge of OHSS facilitates early detection and prevents catastrophic complications, and intensive hospitalized treatment is indicated for serious OHSS. According, neurological deficits with OHSS should be considered as criteria for hospitalization.

Keywords: Ovarian hyperstimulation syndrome; Thromboembolic stroke

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Introduction

The Ovarian Hyperstimulation Syndrome (OHSS) is an iatrogenic complication of Ovulation-Induction Therapy (OIT) for Assisted Reproductive Technology (ART) which is rare but life-threaten in severe form. The prevalence of the severe OHSS ranges from 0.1% to 5% among patients undergoing OIT [1-3]. The pathophysiology remains uncertain. It consists of ovarian enlargement accompanied by overproduction of ovarian hormones and a host of other ovarian vasoactive substances including cytokines, angiotensin, and vascular endothelial growth factor, which alone or in concert produces a state of increased capillary hyperpermeability [4]. Clinical manifestations are varied, such as ovarian enlargement, abdominal distension, ascites, pleural effusion, and electrolyte disturbances. Severe OHSS can lead to multiple organs failure and thromboembolic events [5]. Thromboembolism is rare but serious. A systematic review of literatures included 68 reported OHSS cases, in which 65.7% of thrombi occurred in the venous system, while 34.3% in the arterial system [6]. Thromboembolism in the brain is the most feared complication of OHSS [5,7], despite treatment the neurological deficits with functional disability or even the unfortunate death in productive young women might be happen. Here, a case of OHSS complicated multiple left cerebral infarctions during her first trimester of pregnancy after OIT is documented.

Case Presentation

A 39-year-old, right handed, pregnant woman was admitted to our hospital with the chief complaint of sudden loss of consciousness and right-side weakness. She had undergone OIT with follitropin-beta injection of 200–250 IU for 9 days at a district hospital, 3 weeks before admission. Abdominal distension appeared 1 week after she finished the course of follitropin-beta. OHSS was suspected. Sonography revealed bilateral enlarged ovaries (right 9.7 cm x 9.1 cm; left 7.5 cm

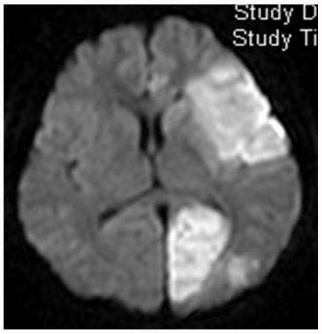

Figure 1: Magnetic resonance imaging of the brain showed multifocal high-intensity lesions on diffusion-weighted imaging, involving the left frontotemporal lobe, insular cortex, and left occipital lobe, suggestive of recent infarcts.

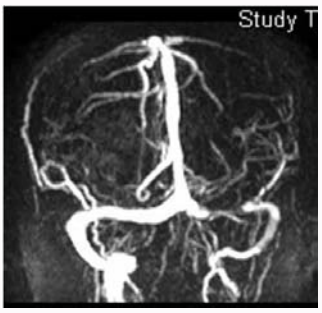

Figure 2: Magnetic resonance angiography showed total occlusion of the left internal carotid artery.

x 4.4 cm), and ascites. Ascites fluid (2,200 ml) was removed by paracentesis. Two days prior admission to our hospital, she had a short episode of syncope and aphasia for hours–after regaining consciousness. She was sent to a district hospital and discharged home on the next day, with a total recovery and negative findings on blood tests. At home, on the day of admission to our hospital, she had another episode of consciousness loss associated with right side weakness. After intravenous hydration with 2,000 ml normal saline at same district hospital, she was transferred to our hospital due to persistent impaired consciousness. On admission, her blood pressure was 126/74 mmHg, with a heartbeat of 102 beats/min and body temperature of 36.8°C. On examination, she was drowsy with severe right side weakness and global aphasia. OHSS with ischemic stroke was diagnosed. Laboratory tests demonstrated that the serum white blood cell counts (18.8 x 10^3/μL; normal, 3.5-11 x 10^3), c-reactive protein (130.62 mg/dL; normal, <5.0), fibrinogen (594 mg/dL; normal, 198-380) and D-dimer (2,006.12 ng/mL; cut-off at 500) elevated, while serum albumin (2.1 g/dL; normal, 3.5-5.5), hemoglobin (11.8 mg/dL; normal, 12-16) and hematocrit (35.0%; normal 36-46) were decreased. Human chronic gonadotropin was 389.5 mIU/mL (not pregnant, <5). Prothrombin time, activated partial thromboplastin time, homocysteine, antithrombin III, C3, C4, protein C, and protein S were within normal limits. Anticardiolipin antibody, antiphospholipid antibody, antinuclear antibody were negative. Transthoracic echography showed no cardiac abnormalities.

Magnetic resonance imaging showed ischemic lesions on T2-weighted and diffusion weighted imaging in the left frontotemporal lobe, insular cortex, and left occipital lobe (Figure 1). Magnetic resonance angiography showed total occlusion of the left internal carotid artery (Figure 2). The patient had no history of hypertension, diabetes mellitus, hyperlipidemia, cardiac abnormalities, illicit drug abuse, and neither family history of thromboembolic disease nor OHSS.

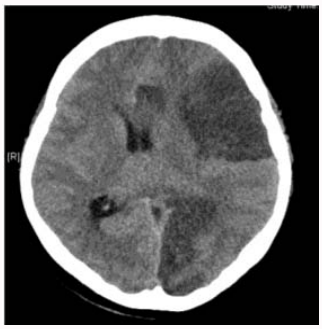

Figure 3: Computerized tomography revealed large infarctions in the left cerebral hemisphere with a midline shift, and subfalcine and uncal herniation.

The patient was admitted to the Intensive Care Unit (ICU). Over the next few days, she received conservative and supportive treatment with IV fluids, albumin and mannitol infusions, with close monitoring of her physical and neurological conditions. Her pregnancy was decided to be terminated after consultation by her medical team with her family on her fourth day in ICU. Unfortunately, she became more lethargic and her right pupil became dilated, without any light reflex on the next day. New neurological deterioration was noted, and emergency brain computerized tomography revealed large infarctions in the left hemisphere causing a rightward midline, uncal herniation, and effacement of the cortical sulci (Figure 3). She underwent a craniotomy and left temporal lobectomy due to neurological deterioration and increased intracranial pressure. Next day, transvaginal echography showed a small gestational sac (maximal diameter, 0.92 cm) without a fetal heartbeat; left ovary measured 10.4 cm x 12.1 cm, right ovary measured 7.4 cm x 6.2 cm, and a small amount of ascites fluid noted in the cul-de-sac. The pregnancy was terminated at 12 weeks of gestation. She was transferred to rehabilitation department 3 weeks after brain operation, with right hemiplegia and global aphasia. After 6 weeks of intensive rehabilitation, she could ambulate with assistance for 10 meters but say only a few words. C-reactive protein, fibrinogen, D-dimer, and albumin returned to normal, and she was discharged with aphasia and poor communication ability. One year after the left hemispheric infarctions, she still had right hemiplegia but can walk independently. Her speech had some improving with few short phrases.

Discussion

There are few reports of cerebral infarction complicating OHSS in the medical literature [5,7-10]. In our patient, the thrombotic events occurred in left carotid artery territory, resulting in multiple cerebral infarctions is rare. This clinical picture differs from the previously reported cases by its extent of the infarctions and the fulminating process. Ovulation induction with daily administration of 200-250 units of Follitropin-beta injection is not a careful treatment regimen though not exceeding the maximal dose suggested by company.

The cause of OHSS associated thromboembolic disease is not clearly understood, but it appears to be related to high estrogen concentrations, low plasma volume, and hemoconcentration [11]. In our patient, a low serum albumin level at admission suggested fluid

shift to the third space, with reduced intravascular volume. Increased levels of fibrinogen and D-dimer were observed on admission and normalized by the follow-up examination with supportive treatment. The presence of progressive, multi-territorial infarctions with alterations of hemostatic factors and the absence of a cardioembolic source, suggested a hypercoagulable state, which could have been responsible for her cerebral infarctions. Her initial hematocrit and hemoglobin were not increased, which could have been partly due to the effect of hemodilution treatment for OHSS at the infertility clinic. However, high estrogen level is an established hypercoagulable state. Antithrombin III, protein C, protein S, anticardiolipin IgG, and antiphospholipid antibody were all within normal limits, excluding other hypercoagulable states.

The treatment of OHSS is aimed at supportive conservative measures to prevent and counter hemoconcentration. Identification of mild to moderate cases of OHSS is essential to prevent the rare, severe complications. Severe OHSS requires immediate therapy under close monitoring. Careful clinical examination to detect the presence of secondary complications is essential for the prevention of severe OHSS [12,13]. Hematocrit is a valuable parameter for evaluation of the severity of OHSS. One criteria for hospitalization is hematocrit rises to 45% form previous literature [6]. According to this case report, we suggest that other clinical neurological symptoms and signs must be considered and combined for hospitalization required. Heparin should be given when the thromboembolic risk is markedly increased, such as with hyperestrogenemia, immobilization, compression of the pelvic vessels by enlarged ovaries or ascites, and pregnancy coagulation anomalies. Prevention of signs and symptoms by the use of mobilization and anti-thrombosis stockings is insufficient because the etiology of thrombosis is of a systemic nature [6]. Furthermore, early treatment with intra-arterial Recombinant Tissue Plasminogen Activator (rt-PA) in OHSS complicated by thromboembolic stroke was reported in a case report, with successful results [7]. This treatment needs a careful evaluation for indicated patients with OHSS complicated thromboembolic stroke to avoid complication, also the time window for aggressive rt-PA treatment is not yet determined. Due to delay diagnosis and large multiple infarctions, the intra-arterial rt-PA was not given in our case. Abdominal paracentesis may be needed for symptomatic relief of tense ascites. It is also indicated in the setting of oliguria, increasing creatinine or decreasing creatinine clearance, and hemoconcentration refractory to medical therapy. Surgical intervention for OHSS should be avoided unless hemorrhage of an ovarian cyst, cystic rupture, or torsion of the ovary is suspected. Termination of pregnancy may be necessary in a few rare cases, especially in those with severe OHSS complications refractory to medical therapy, in an effort to decrease the serum human chronic gonadotropin level [4]. As with our patient, severe OHSS with thrombotic events that worsen after conservative treatment under close monitoring make termination of pregnancy inevitable due to without a fetal heartbeat.

Prophylaxis heparin is debatable since there are no randomized studies proving its efficacy in preventing thromboembolic complications during severe OHSS. Although, heparin was given, thromboembolism was reported in some patients. Besides, the timing for administration is undetermined. Some favor maintaining heparin therapy for at least 4 weeks and even during the whole first trimester of pregnancy, others suggest before the appearance of OHSS symptoms [6]. However, this should be applied to patients with known pre-existing thrombophilic factors. In this case, she was treated without heparin at outside district clinics and due to no known history of thrombophilic factors. Evaluation of antithrombin III, protein C, protein S, and mutation of Factor V, II and MTHFR genes should be performed for patients with a personal and family history of thromboembolic episodes or previous OHSS [6]. The prevention and treatment of OHSS should be individualized or standardized which are still controversial [12,14]. However, early identification of OHSS and thromboembolic risk factors is helpful for prevention and management of thromboembolic events occurring in critical OHSS.

Conclusion

Since ARTs are used much more common for infertility in recent days. Early diagnosis and hospitalization for those rare serious OHSS to prevent further catastrophic or life-threatening complications including the thromboembolic stroke is necessary.

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