Stroke as fatal complication of ovarian hyperstimulation syndrome

Mohammed Talaat Rashid¹, Ahmed Kohail²

¹Saudi German Hospital, Department of Emergency, Madina
²Saudi German Hospital, Department of Neurology, Madina

Abstract
Ovarian hyperstimulation syndrome is a condition related to injectable hormonal medications used for stimulation the maturation of oocytes in infertility caused by lack of or delayed ovarian maturation. The incidence increased due to wide spread expansion of hormonal stimulation use. The scale of symptoms of this condition varies from mild outpatient managed symptoms as vomiting and bloating to sever fatal complication as hemoconcentration, fluid overload, hypercoagulability, and multisystem organ failure. The main point of management is prevention and exclude the candidates with elevated risk of the condition. Here we present a case of 30-year-old woman who had ovarian hyperstimulation syndrome with rare but severe complications.

Keywords: Ovarian Hyperstimulation syndrome, stroke, cerebrovascular accident

Introduction
30 years old female, African, came to Emergency Department (ED) on 24th of August 2016 with recurrent attacks of right sided headache, sudden onset, without aura, associated with nausea and vomiting. There was no blurred vision. These attacks triggered by noise and anxiety and revealed with analgesics. She had no significant past or family history. She had normal vital signs, physical examination and CT brain was unremarkable. She was discharged on oral medication and diagnosed with migraine.

Case Report
On 19th of September 2016, she was following up with an obstetrician for primary infertility for one year. She had irregular cycles, missed period and normal levels of Luteinizing Hormone (LH), Follicular Stimulating Hormone (FSH) and Thyroid Stimulating Hormone (TSH). Trans-vaginal Sonography (TVS) showed normal ovaries with multiple premature follicles. She was started on metformin and clomiphene sulfate as a case of polycystic ovarian disease. On follow up, TVS showed no dominant follicles. Therefore, FSH injections, epigonal, started. After multiple visits, no improvement.

On 4th of February 2017, she was started on norethisterone, primolut-N. Six weeks after that on 15-3-2017, she presented in ED with abdominal pain, nausea, acute increase in body weight, and fatigue. Hemoglobin was 17 and hematocrit was 48. She was diagnosed with Ovarian Hyperstimulation Syndrome (OHSS). She refused admission and discharged on Clexane with explanation about warning signs.

On 18th of March 2017, she presented in ED with acute left sided weakness, upper limb is more affected than lower limb, hypotonia, deviation of mouth to right side, and dysarthria. There were no fits, trauma, Disturbed conscious level, nor fever. Moreover, planter reflex and pregnancy test were positive, hemoglobin was 12 and hematocrit was 33, +3 proteins and +2 bloods in urine. Ultrasonography (US) showed ovarian enlargement with multiple follicles, (33mm) uterine thickness, and marked ascites. Magnetic Resonant Imaging (MRI) of the brain showed right sided basal ganglion and peri-insular area of restricted diffusion, with abrupt termination of right middle cerebral artery. Prothrombin concentration was 90, prothrombin time was 14 and International Normalized Ratio (INR) was 1.0. She was admitted a case of acute ischemic stroke and was treated accordingly. She was discharged on 23-3-2017 with clinical improvement and anti-ischemic medication.

On 24th of March 2017, she was presented in ED with acute onset of headache all over with marked left sided weakness associated with hypotonia and deviation to right side, Glasgow Coma Scale
was 3/15, and unequal pupils. Computed Tomography (CT) of the brain showed right parietal and basal ganglion intracranial hemorrhage (ICH) with bilateral occipital horns intraventricular hemorrhage. She was intubated and mechanically ventilated. She was admitted as a case of ICH with brain conization and announced dead on 28-3-2017 (Figure 1).

**Figure 1.** Computed Tomography (CT) for our patient: Right parietal and basal ganglion intracranial hemorrhage (ICH) with bilateral occipital horns intraventricular hemorrhage.

**Discussion**

Ovarian hyperstimulation syndrome is an iatrogenic complication affects women taking injectable hormonal medications to stimulate oocytes development in the ovaries, which can cause serious psychological and physiological derangement and, in rare cases, may leads to maternal death [1].

The pathophysiology of ovarian hyperstimulation syndrome is not completely understood but it is happening in the ovary exposed to human chorionic gonadotrophin (hCG) or luteinizing hormone (LH) after its stimulation by follicle-stimulating hormone (FSH). This lead to start a cascade of production of proinflammatory mediators from the stimulated like vascular endothelial growth factor (VEGF), interleukins, tumor necrosis factor-α, and endothelin-1. These substances induce increase in vascular permeability and capillary leakage into third space causing the syndrome [2].

Ovarian hyperstimulation syndrome is classified according to severity into mild, moderate and severe. The mild form is manifested by abdominal distention and discomfort with nausea, vomiting, and/or diarrhea, all associated with ovarian enlargement of 5-12 cm. Moderate, is the same as mild plus ultrasonographic evidence of ascites. Severe Ovarian hyperstimulation syndrome has the features of moderate form with clinical picture of ascites and/or pleural effusion and shortness of breath associated with laboratory findings like oliguria (<300 ml/day or <30 ml/hour), hemocrit (>0.45), hyponatremia (<135 mmol/l), hypo-osmolality (<282 mOsm/kg), hyperkalemia (>5 mmol/l), hypoproteinemia (serum albumin <35 g/l). In more critical cases, it is associated with hemocrit (> 0.55) white cell count (>25000/ml), anuria, thromboembolism, acute respiratory distress syndrome, and pre-renal affection [3]. Ovarian hyperstimulation syndrome incidence was found to increase with certain concomitant conditions like migraine and hypercoagulable status. The aim of this case report is to highlight the higher risk of patients with such conditions. Moreover, to urge deeper history taking especially regarding migraine before proceeding for the induction process.

The prevalence of ovarian hyperstimulation syndrome increases when the ovary is overstimulated, as detected by increased number of follicles on ultrasonography and elevated levels of estradiol. The incidence of ovarian hyperstimulation syndrome varies according to the risk factors and the protocols for ovarian stimulation, as it increases with the usage of combine GnRH agonists and gonadotropins compared to gonadotropins alone for treatment. Women of childbearing age only are affected by the syndrome. The frequency is estimated as 8-23% in mild form, 1-7% in moderate form, and 0.25-5% in severe cases [4].

There are plenty of studies that tried to find a way to prevent the occurrence of ovarian hyperstimulation syndrome. However, none of which has shown any significant reduction in the development of the syndrome. On the other hand, the change of the protocol of ovarian stimulation by GnRH from agonist protocol to antagonist protocol demonstrates significant reduction in the incidence of sever form of ovarian hyperstimulation syndrome [5].

Treatment of Ovarian hyperstimulation syndrome based on severity of the symptoms. The treatment of mild form is supportive like increase fluid intake and analgesia, and observation for progression to moderate or severe.

Treatment of moderate ovarian hyperstimulation syndrome is also bed rest, adequate fluids intake and monitoring of both, the size of cysts by ultrasonography and serum electrolytes, hematocrits and creatinine.

Management of Ovarian hyperstimulation syndrome mandates bed rest, frequent physical examination and fluid balance. Moreover, maintaining intravascular blood volume, electrolyte balance and managing complications like ascites and hydrothorax. Prevention of thrombosis also should be considered [6].

In more sever and critical Ovarian hyperstimulation syndrome, like with end organ damage, thromboembolism and Acute respiratory distress syndrome, requires intensive [7].

**Conclusion**

Ovarian hyperstimulation syndrome is a condition related to hormonal medications used for oocytes maturation, it is associated with mild manifestations and, rarely, with sever and fatal complications. We recommend detailed personal and family history to uncover any red flags that can make the choice of injectable hormonal therapy for ovarian stimulation contraindicated and consideration of alternative therapies is essential as in migraine, hypercoagulation conditions, or previous history of thrombosis. On the other hand, once ovarian hyperstimulation syndrome is suspected or diagnosed, hydration, anticoagulation with rest, frequent physical examination and fluid balance. Moreover, to urge deeper history taking especially regarding migraine before proceeding for the induction process.
Competing interests
The authors declare that they have no competing interest

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