Case Report

DEEP VENOUS THROMBOSIS AND THROMBOEMBOLIC STROKE RESULTING FROM SEVERE OVARIAN HYPERSTIMULATION SYNDROME (OHSS) AFTER IN-VITRO FERTILIZATION

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Abstract

Background: Ovarian Hyperstimulation Syndrome (OHSS) is a rare complication following hormonal therapy during ovulation induction, which can be life threatening in its severe forms. It can manifest in several ways and affect various systems in the body due to increased thrombotic events in the blood vessels. In its milder forms, patients with OHSS can be managed with both pharmacological and supportive treatments. However, severe forms of OHSS especially cerebrovascular complications, have often proven fatal resulting in severe functional impairments and increased mortality.

Case description: In this report, we review a young woman with background PCOS who presents with OHSS following hormonal induction therapy. Despite pharmacological and supportive management, she eventually developed a stroke in the right cerebral hemisphere following a popliteal and femoral DVT leading to neurological impairment including left facial palsy and left hemiparesis. Significant clinical improvement was observed upon commencement of anti-coagulants, statins and physical therapy and patient was discharged afterwards. Unfortunately, further progress could not be ascertained as patient was lost to follow-up.

Conclusion: Acute ischemic stroke must be considered in females with neurological dysfunction and recent ovarian stimulation.

Keywords: Deep venous thrombosis, Thromboembolic stroke, Ovarian Hyperstimulation Syndrome, Assisted reproductive technology, Ovulation induction.

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INTRODUCTION

Ovarian Hyperstimulation Syndrome (OHSS) is a serious iatrogenic complication of hormonal treatment for induction of ovulation which is rare but can be life threatening in its severe form.[1,2] Although Assisted Reproductive Techniques (ARTs) offer safe procedures for infertile couples, there are also several risks involved – with numerous morbidities and rarely, mortalities.[3] The rate of occurrence for severe forms of OHSS ranges from 0.25 – 5%, especially for patients undergoing ovulation induction therapy.[3,4] Although the exact pathophysiology remains unknown, an interplay of several ovarian factors including hormones, ovarian vasoactive substances (cytokines, angiotensin and vascular endothelial growth factor) are implicated. Characteristic pathophysiological mechanisms of OHSS includes massive fluid shift from the intravascular space into the peritoneal cavity resulting in haemoconcentration with increased blood viscosity, leading to both arterial and venous occlusions.[5,6]

Beta human chorionic gonadotropin (hCG) and its analogs play a critical role in ovarian angiogenesis. These analogs can trigger a cascade pathway, contributing to increased permeability in the vessels and increased interstitial fluid.[7] The clinical manifestations of OHSS are varied. Ascites, ovarian enlargement, abdominal

distention, pleural effusion and electrolyte derangements are seen in patients presenting with OHSS.[1,5] Severe forms of OHSS can manifest with acute respiratory distress syndrome (2%), renal and liver failure (1%) and even thromboembolic events.[8] Thromboembolism is the most serious complication of OHSS, with cerebral thromboembolism as the most feared complication.[1] In a literature review evaluating the prevalence of thromboembolism phenomena in OHSS, 75% of the thrombotic events are of venous origin and the rest of arterial origin.[5,9] In spite of medical interventions, including pharmacological treatment; patients with cerebral thromboembolism might progress with neurological and functional impairments.[1]

Few cases of cerebral arterial infarct are reported in literature, especially in Nigeria. Here, we report a case of right middle cerebral artery (MCA) stroke with deep vein thrombosis (DVT) of the right popliteal and femoral veins following OHSS after in-vitro fertilization (IVF).

CASE DESCRIPTION

A 29-year-old, right-handed nulliparous woman with background polycystic ovarian syndrome, undergoing IVF for infertility presented to the emergency room on account of abdominal pain, abdominal swelling and vomiting. She had undergone ovulation induction with intramuscular (IM) Buserelin, IM Menotropin and Gonal F at a fertility clinic prior to presentation. Abdominal swelling had progressively increased in size and necessitated insertion of a Bonnano catheter which she presented with. Physical examination was significant for ascites and paraumbilical tenderness with a blood pressure of 106/60mmHg. Basic relevant workup showed elevated white cell count (19.2x 10^9/L; Ref. range: 4-11 x 10^9/L), hypoproteinemia (Total Protein: 48g/L; Ref. range: 60 -80g/L), hypoalbuminemia (Albumin conc: 21g/L; Ref. range: 32-50g/L) and hyponatremia (132mmol/L; Ref. range: 135 –145mmol/L).

On arrival, an assessment of critical OHSS was made and she was started on subcutaneous Enoxaparin Sodium in addition to IV fluids, antibiotics, antiemetics and analgesics. On the 3rd day, the patient developed severe pain and swelling in the right lower limb with slight deviation of the mouth to the right and inability to move the left limbs. Laboratory investigations revealed worsening hypoalbuminemia (16g/L; Ref. range: 32-50g/L), anemia (23%; Ref. range: 35%-45%), deranged LFT values (AST: 656 U/L, Ref. range: 5-40U/L; ALT: 303 U/L, Ref. range: 7-50U/L; GGT: 230 U/L, Ref. range: 5-40U/L; ALP: 394 U/L, Ref. range: 44-147U/L) and thrombocytosis (707 x 10^9/L, Ref. range: 150 x 10^9/L - 450 x 10^9/L)

Brain CT scan done showed extensive acute right hemispheric infarct over the right parietal lobe indicative of a main trunk middle cerebral artery occlusion (Figure I). Duplex Ultrasound scan of the right lower limb revealed popliteal and femoral deep venous thrombosis with no arterial embolus. Review by the Neurologist was remarkable for a left gaze palsy with left upper motor neuron facial palsy, left hemiparesis accompanied with sensory inattention of the left side of the body. D-dimer result showed an elevated value of 6139.9ng/ml (Ref. range: <250ng/ml) however, PT/INR and APTT were normal. An assessment of right hemispheric ischemic stroke, most likely thrombotic, triggered by hypercoagulable state from overstimulation of ovaries was made. She was commenced on oral Rivaroxaban, IV fluids, anti-platelets and statin therapy. She was referred for daily physiotherapy sessions and encouraged on high protein diet with liberal oral intake. Abdominal drain remained active with a total of 9,200mls over four days and then gradually began to decline in daily output. Daily abdominal drain continued to trend downward, averaging about 70mls/day after which the catheter was taken out. Patient showed significant functional improvement (Power Grade: Left Upper limb – 2/5; Left lower limb – 3/5). Repeat PT/INR was 1.7 (Ref. range: 2.0 – 3.0) with further drop in white cell count to (9.2x 10^9/L; Ref Range: 4.0 x 10^9/L – 11.0 x 10^9/L). The patient was discharged, to be followed up on outpatient basis. Unfortunately, this patient was lost to follow up.

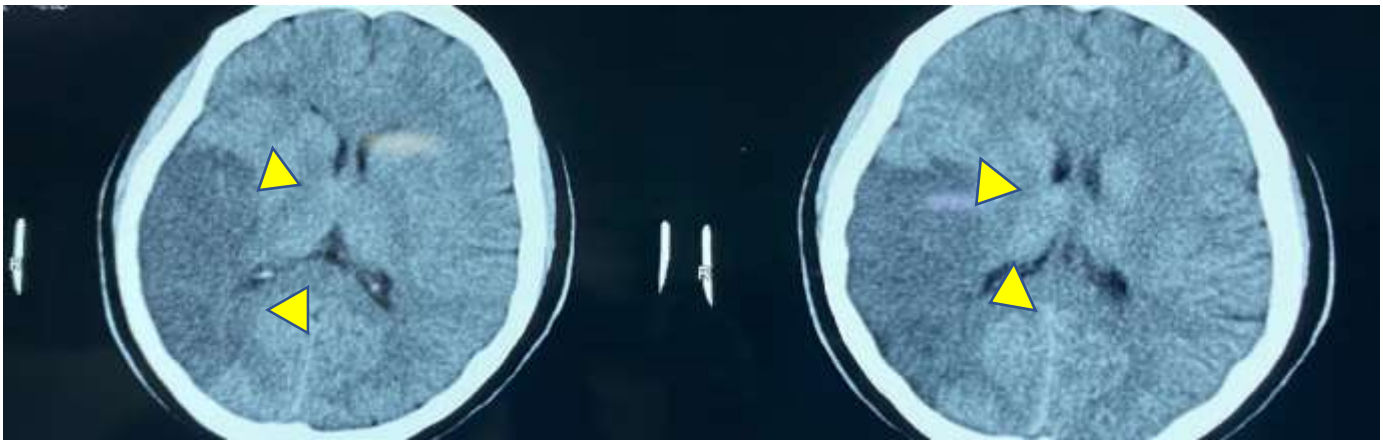

Figure I: Computed Tomography scan showing extensive hypodense lesion in the right parieto-occipital lobe (yellow arrow heads)

DISCUSSION

Although rare, severe OHSS is a serious iatrogenic consequence of medical induction of ovulation with hormones for fertility treatment occurring during the luteal phase. The reported incidence is about 0.25 – 5%.[3,4] There are few reports of OHSS complicated by cerebral infarction which may result from severe forms of OHSS thus leading to remarkable morbidity and mortality.[10] Studies have shown that there is a likelihood of under reporting by practitioners.[11]

Ovarian hyperstimulation syndrome is a well described complication of fertility treatment which uses pharmacological means of stimulating the ovaries to increase the number of oocytes available during assisted reproductive technology. It is usually associated with the exogenous gonadotropin administration. Existing risk factors which are likely to increase the magnitude of response to stimulation of the ovaries include: young age (<35 years),[12] polycystic ovarian syndrome,[13] previous OHSS,[12,13] use of gonadotropin releasing agonist (GRA) protocol,[12,14] absolute levels or rate of increase of serum estradiol,[12,14] follicular size,[14] number of oocytes stimulated, higher or repeated dose of exogenous hCG and number of oocytes retrieved.[13,14] Our patient was 29 years old with polycystic ovaries who underwent a GRA protocol for oocyte retrieval, although the exact number of oocytes retrieved was uncertain.

OHSS is classified into mild, moderate and severe[15] with a severity grading from 1 – 6 based on ovarian size and associated symptoms. Severe cases of OHSS are characterized by enlarged ovaries with significant cyst formation, massive ascites, electrolyte imbalance, hypovolemia, increased blood viscosity from hemoconcentration, coagulation abnormalities and decreased organ perfusion especially in the kidneys and liver. Less than 2% of severe OHSS cases are associated with thromboembolic events including venous occlusive and arterial diseases.

The pathophysiology of thromboembolic disorders resulting from OHSS is not well understood but it may be due to vasoactive mediators secreted in excess by hyper-stimulated ovaries. Recent studies have identified a relationship between OHSS and vascular endothelial growth factor (VEGF) as major mediator of OHSS pathophysiology, playing a crucial role in follicular growth, corpus luteum function and ovarian angiogenesis. It also stimulates endothelial cell proliferation, cell permeability and angiogenesis.[16]

It is of importance to note that not all cases of thromboembolism after stimulation of the ovaries have association with OHSS and not all patients with OHSS develop thrombosis.[3] Other reported predisposing factors which increase the risk of thrombus include antithrombin III,[17] activated protein C,[18] protein S deficiency[19] and factor V mutation.[20] In the few cases of cerebral arterial infarction secondary to OHSS that has been reported in the medical literature, majority of thrombi occur in the

middle cerebral artery territory which is similar to the artery involved in this report.

This patient was also commenced on thromboprophylaxis however, this was not effective in preventing the thromboembolic event that occurred. There have been reported cases of thrombosis following OHSS despite anticoagulation prophylaxis.[21,22] Although it has been reported that LMWH might be beneficial in severe cases of OHSS,[21,22] it is still controversial whether to or not to screen women undergoing ART for thrombophilia (personal and family history). In our patient, hypoalbuminemia and hypoproteinemia were observed on admission and both suggested fluid shift to the third space with reduced volume in the intravascular space. Elevated D-dimer was also noticed on admission – all of which were in keeping with features of critical, grade 6 OHSS.

It was not clear in this case whether the cerebrovascular accident was as a result of deep venous thrombosis or another isolated thrombus in the middle cerebral artery as the patient did not have an echocardiography to rule out cardiac septal defect or angiography to know the extent and level of blockade. The patient was also not screened for other risk factors of thrombosis to exclude any underlying prothrombotic abnormality.

The management of OHSS depends on the severity and majorly involves supportive measures which includes intravenous hydration, administration of human albumin and electrolyte correction thus helping to decrease hypovolemia and hemoconcentration which ultimately decreases the risk of a thromboembolic event. Emphasis should be placed on the prevention of OHSS because thromboembolism could be a progression of severe OHSS which is consistent among reported literature.

Early treatment with intra-arterial recombinant tissue plasminogen activator (rt-PA) has shown favorable outcomes in the management of severe OHSS, however contraindicated in pregnancy because of its perceived role in placental disruption but may be warranted in the face of significant morbidity and mortality.[23]

There are still some controversies regarding the standardized measures for preventing and treating OHSS, however some beneficial preventive measures to reduce the risk of OHSS include: ovarian stimulation with low dose gonadotrophins for a longer period, no hCG for ovulation induction, timed early follicular aspiration, albumin therapy at the time of follicular aspiration, elective freezing of all embryos, in vitro maturation of immature oocytes from unstimulated ovaries of women with PCOS and cycle cancellation and withholding hCG.[24, 25] Early identification of OHSS and risk factors for thromboembolism is highly crucial and helpful for the prevention and management of thromboembolic events during severe OHSS.

CONCLUSION

Ovarian hyperstimulation syndrome is the most serious iatrogenic complication associated with ovulation induction or multifollicular development for in-vitro fertilization. The symptoms of OHSS are unspecific and the clinical diagnosis has been classified into various grades based on its severity as mild, moderate and severe. Given that strokes are typically a progression of severe OHSS, prevention of the syndrome itself would be an expedient approach. Thrombophilia screening prior to the initiation of fertility therapy might be considered sensible in the risk assessment of thromboembolic events but is unlikely to be cost-effective.

Acute ischemic stroke must be considered in females with neurological dysfunction and recent ovarian stimulation.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the draft and final version of the manuscript.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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