Jugular Vein Thrombosis and Recurrent Pleural Effusions in OHSS

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Abstract

Background: Ovarian hyperstimulation syndrome remains a significant cause of morbidity in ovulation induction. It may be further complicated by thromboembolism and pleural effusions.

Case Report: A 30-year-old nulligravida underwent ovarian stimulation with OCP/Antagonist protocol for *in vitro* fertilization. Estradiol levels peaked at 2411 pg/mL. Post-stimulation course was complicated by recurrent pleural effusions and an occlusive right internal jugular vein thrombosis. The patient underwent repeated thoracenteses with a drainage of a total of 8350 cc of pleural fluid. The patient received therapeutic anticoagulation and delivered a viable infant at term. Imaging at six weeks postpartum revealed a chronic, non-occlusive deep venous thrombosis involving both the right internal jugular and right subclavian veins.

Conclusion: OHSS results in dynamic changes that contribute to thrombosis and massive fluid shifts. Further research is needed to optimize prevention strategies.

Key Points

- Thromboembolism and pleural effusions remain a significant cause of morbidity to patients undergoing ovarian stimulation.

- Incidences of thrombosis varies from 0.2-10% among *in vitro* fertilization cycles and occur most frequently in the upper body secondary to estradiol concentration in the lymphatic system.

- Optimizing outcomes for these patients requires high clinical suspicion and an interdisciplinary approach.

Introduction

Ovarian hyperstimulation syndrome is almost exclusively an iatrogenic complication of assisted reproductive technology. In very rare cases, it may occur spontaneously, including in women with mutations in the Follicle-Stimulating Hormone (FSH) receptor [1,2]. The overall incidence of OHSS is estimated at 0.6-14% [3]. Incidence can be further subdivided by severity, with moderate OHSS estimated at 3-6% of treatment cycles and the severe form affecting only 0.1-3% [4]. Its exact pathophysiology remains elusive, but it is largely categorized by fluid shift out of the intravascular space resulting in hemoconcentration and hypovolemia.

An exaggeration of physiologic processes, OHSS occurs in stages. Initially, small antral follicles are recruited into large follicles which secrete Vascular Endothelial Growth Factor (VEGF), resulting in peri-follicular neovascularization and increased permeability. VEGF has been implicated in OHSS with a mechanism of action dependent on Human Chorionic Growth Hormone (HCG), which affects cell-to-cell adhesion complexes in the endothelium [5-7]. The resulting neovascularization and vascular permeability result in intravascular hypovolemia with subsequent edema, ascites, hydrothorax and even hydropericardium. The massive fluid shift into the third space can have varying degrees of impact on the patient. In its mild, and most common form, fluid shifts are limited to the peritoneal cavity where nausea and discomfort are common and expectant management is usually sufficient. When ascites is evident on ultrasound, the disease is categorized as moderate and symptoms feature those of mild OHSS in addition to hypoproteinemia, elevated hematocrit and leucocytosis [8].

Severe OHSS features hypovolemia, oliguria, intractable nausea and vomiting, in addition to biochemical derangements including elevated creatinine, hematocrit >55%, significant leukocytosis and transaminitis [9]. Hypovolemia leading to hemoconcentration and depletion of anti-clotting factors increase the risk for thromboembolism [10]. The incidence of thrombosis is estimated at 0.2% to 10% in cases of ovarian hyperstimulation syndrome [11].

Case Report

Our case is a 30-year-old nulligravid woman who underwent ovarian stimulation for her first IVF cycle. She tried to conceive for two years, including two unsuccessful monitored ovarian stimulation cycles with letrozole followed by intrauterine inseminations, with a final diagnosis of male-factor infertility secondary to oligoasthenoteratozoospermia. She underwent ovarian stimulation with OCP/Antagonist protocol using ganirelix acetate. Estradiol levels at initiation of FSH stimulation were 175 pg/mL, with a level of 2309 pg/mL on the day of trigger with human chorionic gonadotropin. Prior to egg retrieval, estradiol levels peaked at 2411 pg/mL and multiple follicles were visualized on the right ovary, with 10-12 follicles visualized on the left ovary. Nineteen oocytes were retrieved, and four blastocysts were cryopreserved, and one blastocyst was transferred.

On post-transfer day one, she presented with a one-pound weight gain and complained of abdominal distention, shortness of breath and chest pain. Pelvic ultrasound showed 6 cm pockets of fluid in the pelvis bilaterally and multiple corpora leutea, and the ovaries measured 7.4 cm (right) and 9.5 cm (left). By post-transfer day 14, estradiol levels had risen to 3499 pg/mL and her pregnancy test was positive with a beta-hCG was 596. Of note, thrombocytosis ($562 \times 10\,E^3$/uL) was noted at that time. Transaminases were elevated: AST 50 IU/L, ALT 58 IU/L. However, hematocrit remained normal at 41.6%. On post-transfer day 16, the patient presented with a 11pound net weight gain, worsening

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abdominal distension, shortness of breath, decreased intake as well as nausea and vomiting. Ultrasound showed a large amount of fluid in the pelvis, bilaterally enlarged ovaries, and a viable intrauterine pregnancy with cardiac activity. She was admitted for thoracentesis when found to also have a large, right pleural effusion. She underwent three therapeutic thoracentesis as an outpatient with removal of 2950 cc of clear fluid with significant, but temporary, improvement in her symptoms. No prophylactic anticoagulation was administered, and she received oral hydration throughout her multiple thoracenteses.

By post-transfer day 23, the patient presented with worsening shortness of breath and tense ascites and complained of neck swelling. Duplex ultrasonography of the bilateral upper extremity central veins revealed an acute, occlusive deep venous thrombosis involving the right internal jugular vein. She was promptly admitted as an inpatient and CT-angiogram at that time showed large pleural effusions and no pulmonary embolism. She was acutely treated with therapeutic anticoagulation on a heparin drip, and also underwent two more thoracenteses with removal of 2400 cc of clear fluid. She was then transitioned to low-molecular weight heparin 1 mg/kg twice daily with improvement in neck swelling. OHSS was deemed to be the inciting factor for thrombus formation in this patient. As her pregnancy progressed, she continued anticoagulation on low-molecular weight heparin. She delivered a viable female infant via elective caesarean section at 39 weeks. At six weeks postpartum, duplex ultrasound revealed a chronic, non-occlusive deep venous thrombosis involving the right internal jugular and right subclavian veins that remained stable. Anticoagulation was discontinued at that time.

Discussion

We describe a case of a woman with a severe and rare complication of OHSS which required treatment throughout her pregnancy and postpartum period. As previously mentioned, thrombosis represents the most dangerous complication of OHSS. Those affected are typically young, healthy patients whose illness imposes a significant socioeconomic burden [12-14]. Understanding how anatomy contributes to thrombosis in OHSS is vital to enhancing clinical suspicion. Thromboses in OHSS are commonly venous (65-75%) and involve the upper limbs and neck. The most common sites being the internal jugular and subclavian veins [12]. Arterial thrombosis occurs at a rate of 25-33% and tends to be intracranial [15]. The tendency for upper body thrombosis is explained by lymphatic anatomy and drainage. Ascitic fluid with very high concentrations of estradiol is collected from the peritoneal space and further concentrated into the cisterna chyli, transported to the thorax via the thoracic and lymphatic ducts and ultimately drained into the systemic circulation at the junction between jugular and subclavian veins. The result is a localized, thousand-fold increase in estrogen levels. This leads to excessive local activation of the coagulation cascade and is a potent stimulus for thrombus formation at these anatomical sites [16,17]. In addition to its direct procoagulant effects, estradiol is thought to decrease local concentrations of thrombomodulin, which functions as a cofactor in thrombin-induced activation of protein C, thus leading to impaired downregulation of thrombin formation and an increase in thrombotic events [18,19].

Internal Jugular Vein (IJV) thrombosis may occur at any point along the intracranial internal jugular vein to where it meets the subclavian vein and forms the brachiocephalic vein. In the general population, it is most commonly a complication of infection, malignancy, thrombophilias, central venous catheters, intravenous drug use and surgery. The complications of an IJV thrombosis are serious and

life-threatening, and include pulmonary embolism, chylothorax and respiratory collapse. A high degree of clinical suspicion is essential to diagnosis and expediting treatment. The most common symptoms at presentation are fever, leukocytosis and neck swelling. Our patient presented with neck swelling but was not febrile and did not have a leukocytosis (WBC 11.0 K/uL). Duplex ultrasound showed an acute, occlusive right internal jugular vein thrombosis (Figure 1) in addition to a large bilateral pleural effusion (Figure 2). She was given an initial dose of therapeutic lovenox, then switched to a heparin drip for anticoagulation and to facilitate thoracentesis. Her shortness of breath resolved, and she was discharged home. It is important to note that this patient was well known to both the interventional radiology and pulmonology services, whom worked with the primary team to expedite effective and prompt treatment of this patient. Vascular surgery was also consulted and followed the patient through the postpartum period. At six weeks postpartum, therapeutic anticoagulation on lovenox was discontinued as the effects of the inciting factors-ovarian hyperstimulation syndrome, hypercoagulable state of pregnancy-were deemed complete. A thrombophilia workup was not performed for this reason (Figure 3).
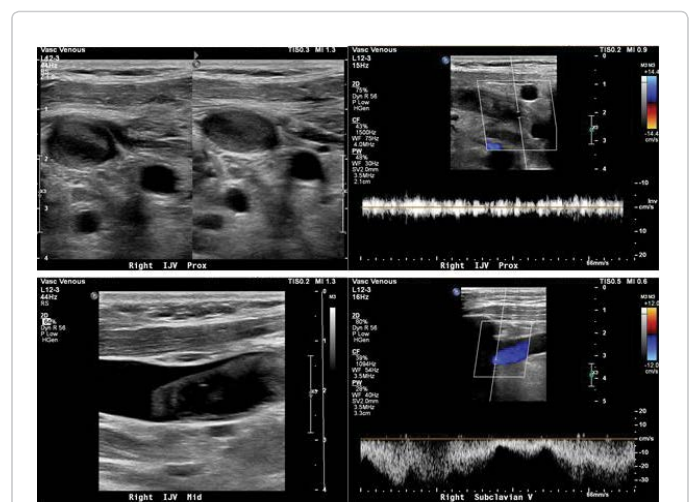

Figure 1: Initial duplex ultrasound showing absent compressibility of the right proximal internal jugular vein with hypoechoic, occlusive thrombus present.
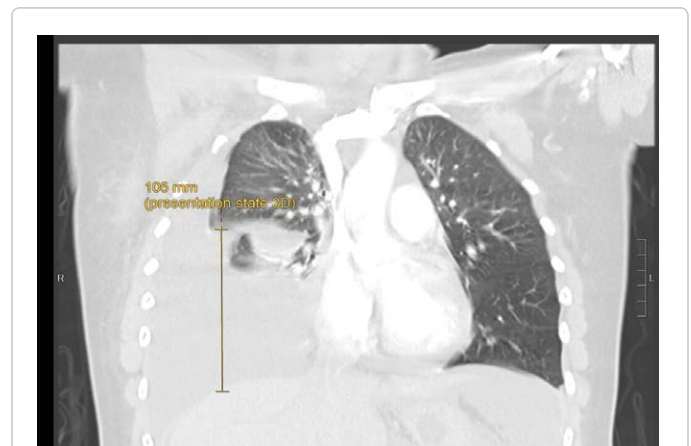

Figure 2: CT imaging showing right pleural effusion measuring 10.5 cm in layers posterior, and left pleural effusion measuring 5.3 cm in layers posterior, Subsequent thoracentesis removed 2400 cc of clear pleural fluid.
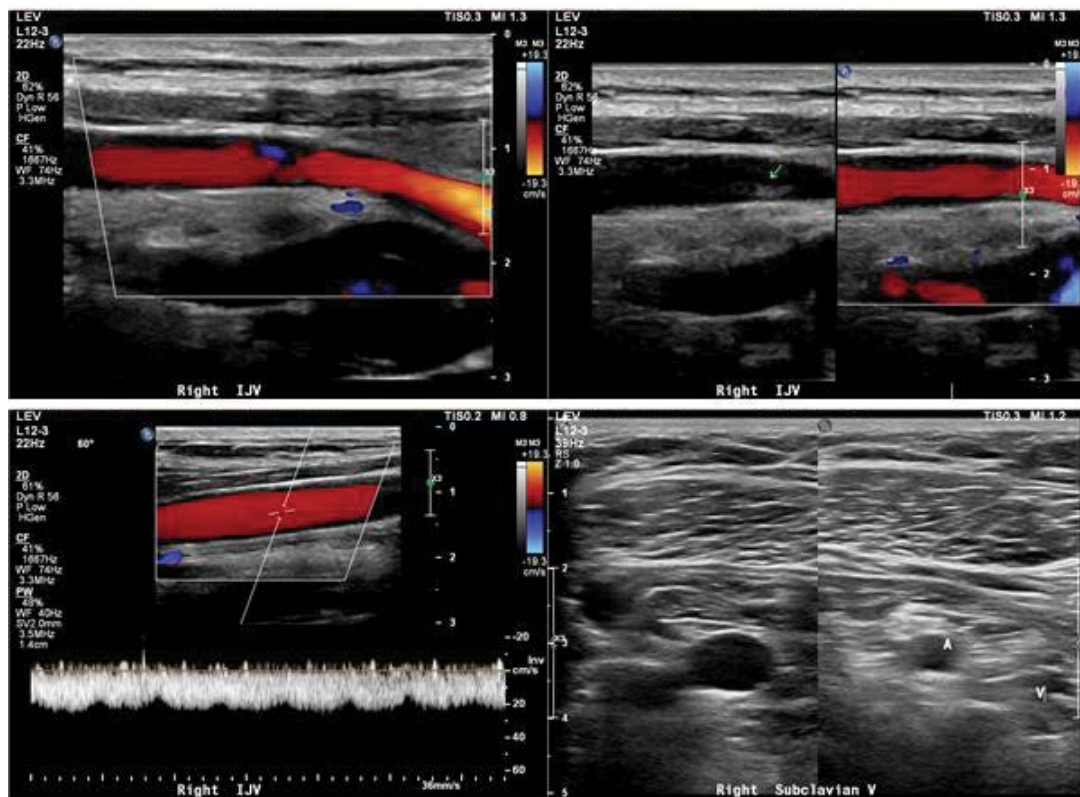
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Figure 3: After six weeks of therapeutic postpartum lovenox, duplex ultrasound revealed a chronic, non-occlusive deep venous thrombosis involving the right internal jugular and subclavian veins, There was no evidence of deep venous thrombosis in the left upper extremity.

Different clinical and laboratory factors have been indicted as causal in thrombosis secondary to OHSS, however no specific diagnostic test has been shown to be superior. The iatrogenic nature of OHSS is paired with an inherent need for prevention strategies, but these are patient specific, and require further research to develop evidence based protocols. Decreasing the overall risk of OHSS will decrease the downstream sequelae, including thrombosis. Prevention strategies can be divided into two broad categories. Recognizing innate risk factors is a primary prevention strategy and includes low body weight, polycystic ovarian syndrome, prior history of OHSS, and young age. In this group, prevention is aimed at decreasing a pathologically exaggerated ovarian response. Strategies including unifollicular ovulation for those undergoing monitored ovulation induction, opting for leuprolide trigger shot, considering GnRH antagonists versus agonists, and utilizing aromatase inhibitors for ovulation induction [20-23]. Women with a known exaggerated response to ovarian stimulation benefit from secondary prevention strategies, including cryopreservation of embryos to eliminate or decrease the number of future stimulation cycles, cycle cancellation, and coasting: A prevention strategy aimed at withholding hCG trigger until estradiol levels plateau or return to non-critical levels [24,25]. Although a GnRH antagonist cycle was used in this particular case, it is debatable if the patient would have benefited from a GnRH agonist trigger and an embryo cryopreservation cycle based on her age and diagnosis of male factor infertility. A high index for suspicion and a multidisciplinary team approach improved her treatment and recovery.

Conclusion

OHSS remains a severe risk to patients undergoing ovarian stimulation, including a risk for venous thromboembolism that affects the post-stimulation course and may affect perinatal management. Patient outcomes are improved by high clinical suspicion and swift management. With improving oocyte/embryo cryopreservation techniques should otherwise young and healthy patients be offered a GnRH agonist trigger and cryopreservation cycle? Optimization of current and elucidation of new prevention strategies are needed and warrant further research.

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