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Case Report

Ovarian hyperstimulation syndrome and development of pulmonary embolism in pregnancy: case report

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Key Words*:* ovarian hyperstimulation syndrome, pulmonary embolism, anticoagulation, venous thromboembolism, assisted reproductive technology (ART), ovarian stimulation, ovulation induction

Abstract: Ovarian hyperstimulation syndrome caused by assisted reproductive technology can lead to pulmonary embolism, a rare but serious side effect.

Case Presentation

A gravid 21 year old G1P0 was admitted to the local emergency room 2 days s/p in vitro fertilization (IVF) embryo transfer (cycle #2) with shortness of breath. She also had abdominal distention, bloating and nausea at that time. Her initial lab work-up showed hemoconcentration and elevated D-dimer (Table 1). She had a chest CT scan in the ER that revealed a right pulmonary embolus (PE) and small right pleural effusion. The patient was started on an unfractionated heparin drip and was transferred to our hospital for further care. Upon admission to our institution, the patient was tachycardic but appeared in no acute distress. The patient was started initially on low molecular weight (LMW) heparin at 1mg/kg (100mg) BID for anticoagulation and her unfractionated heparin drip was discontinued.

The patient's history was complicated by primary infertility due to a combination of oligoovulation and male factor. Her medical history is significant for polycystic ovary syndrome and obesity. Her situation was also complicated by male factor infertility. She is a lifelong non-smoker. She had used oral contraceptive pills for one year prior to attempting to conceive.

The patient had a baseline ultrasound that showed polycystic ovaries (Table 2). She was started on the following protocol for ovulation induction: leuprolide 1 mg on, FSH 150 units, and metformin. The plan for insemination was intracytoplasmic sperm injection (ICSI). Her first cycle resulted in four oocytes retrieved and inseminated by ICSI; one embryo was transferred but did not result in pregnancy. For her second cycle, 16 oocytes were retrieved and six inseminated by ICSI. One embryo was transferred on cycle 2.

Two days after embryo transfer, the patient had nausea and vomiting and was given promethazine. The following day she was admitted to the local

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hospital with shortness of breath and was diagnosed by CT scan with the PE. She was treated with LMW heparin at 100 mg BID, which was continued as an outpatient. Her lab values showed hemoconcentration (Table 1), and this combined with her clinical presentation gave her the diagnosis of severe ovarian hyperstimulation syndrome (OHSS).

On day 15 post-conception, the patient had a positive pregnancy test with quantitative beta-hCG 48 (table 1). Ultrasound done two weeks later showed enlarged ovaries bilaterally, consistent with OHSS (table 2).

Table 1 (laboratory values, *abnormal)

Initial presentation to ER:	
Creatinine	1.3
Hemoglobin	17.8*
Hematocrit	51%*
D-dimer	811*
Quantitative hCG	13
Positive pregnancy test:	
Quantitative hCG	48
Progesterone	229
Estradiol	>200
Hypercoaguability workup:	
Anticardiolipin antibody	IgM 10.1 mpl, IgG 4.8 gpl (normal)
Beta-2-glycoprotein	IgM 4.1 smu, IgG 2.3 sgu (normal)
Dilute viper venom assay	Within normal limits (40 seconds corrected)
Factor V Leiden	No detected mutations

The patient's pregnancy progressed well until she was diagnosed with mild preeclampsia at 35 weeks gestation. She presented with blood pressures in the 140s/90s and a 24 hour urine protein of 395 mg. There was no evidence of renal insufficiency, thrombocytopenia or elevated liver transaminases. Patient was transitioned to unfractionated heparin (dosed every 8 hours) at the time of admission and LMW heparin was discontinued. The patient had a rapid response to heparin, and her dosing was adjusted daily (Table 3). A thrombophilia work-up was done during her admission and found to be negative (Table 1). The patient underwent labor induction at 37 0/7 weeks and was delivered by primary low transverse cesarean delivery at 37 1/7 weeks gestation for failure to descend. Her heparin was stopped 12 hours prior to delivery.

Table 2 (ultrasound results)

Pre-assisted reproductive technology

	Size: (L x W x H)	Volume:	Antral Follicles:
Left Ovary	42 x 29 x 26 mm	17 cc	28
Right Ovary	43 x 33 x 27 mm	20 cc	22

Ultrasound post-ICSI and positive pregnancy test

	Size (L x W x H):
Left Ovary	128 x 79 x 84 mm (enlarged)*
Right Ovary	135 x 96 x 77 mm (enlarged)*
	Multiple corpus luteum cysts
Assigned gestational age:	5 5/7 weeks gestation

Table 3 (Anticoagulation response)

Heparin Dose:	*PTT* following 24 hours Heparin dose:*
Initial dose 12,000 units TID	105
Decreased to 6,000 units TID	48
Increased to 7,000 units TID	59
Continued 7,000 units TID	69-80

**PTT – partial thromboplastin time (Goal 60-80)*

Postpartum she received 24 hours of magnesium sulfate therapy for seizure prophylaxis and was started on therapeutic doses of LMW heparin 12 hours postpartum. She had an episode of heavy bleeding from her incision on postoperative day 3. Superficial exploration showed intact fascia and generalized bleeding from subcutaneous vessels that were cauterized and sutured. Her anticoagulation was discontinued. She was transfused 3 units of packed red blood cells and was discharged on postoperative day 6 from her cesarean delivery without anticoagulation therapy. The decision was made to not anticoagulate her on discharge because she had received 6 months of therapy following her PE, and the inciting factor of OHSS had since resolved. She will receive the Mirena IUD for contraception at her 8 week postpartum visit.

Discussion

Approximately 20.5 million people worldwide are currently seeking medical care for infertility, including assisted reproductive technology (ART). It is estimated that the prevalence of short-term complications of ART is 2%, with ovarian hyperstimulation syndrome (OHSS) accounting for half of all complications. OHSS can be a complication of any medication used for ovulation induction and is most common with the use of gonadotropins or clomiphene citrate.[1] The majority of studies estimate that clinically relevant OHSS occurs in up to 10% of cycles with 2% of these cases being life-threatening or severe.

OHSS is mostly a direct consequence of excessive follicular response to stimulation of the ovaries by pregnancy-induced endogenous hCG elevations or exogenous hCG administration.[2] The underlying mechanism of OHSS is not entirely known. However, this excessive follicular stimulation and the release of vasoactive substances have been shown to lead to third-space fluid accumulation and hemoconcentration leading to hemodynamic and respiratory alterations. These alterations can lead to thromboembolic phenomena.[3] The main mechanism of third-space fluid accumulation is thought to be due to increased vascular permeability. However, several ovarian factors such as the rennin-angiotensin system, cytokines, or vascular endothelial growth factor (VEGF) have been thought to play a role.[4] It is important to diagnose polycystic ovaries (PCO) prior to ovarian stimulation because these patients are more likely to develop OHSS. The risk of OHSS in PCO patients can be minimized by using a low-dose gonadotropin regimen as opposed to high-dose regimen.[2]

Recently, VEGF has been found to play an important role in the pathophysiology of OHSS because it leads to increased vascular permeability in the ovary. There is increasing evidence that VEGF

concentrations increase the risk, incidence and course of OHSS.[5] Dopamine binding to the VEGF receptor has shown to cause an inhibition of VEGF signaling, therefore leading to decreased vascular permeability. The use of cabergoline, a dopamine agonist, has been found to prevent OHSS when used prophylactically during ART without having an adverse effect on the outcome of ART. However, this data has not been extensively studied.[1]

The increased risk of thrombosis found in OHSS is related to several factors. A strongly recognized mechanism is hemoconcentration, leading to elevated blood viscosity and vascular stasis due to decreased flow of the blood stream. Venous thromboembolism is thought to occur more commonly than arterial thrombosis (75 and 25%, respectively).[1] The majority of venous thromboses in patients with OHSS occur in the upper limb, neck and head veins (60%). This is the opposite of venous thromboses found in the non-pregnant population, where majority of venous thromboses are found in the lower extremities. This could be due to estrogen-rich lymphatic drainage from ascitic fluid into the thoracic duct.[6] There is approximately a 4-12% associated risk in these patients of developing pulmonary embolism. As opposed to venous events which can occur up to several weeks after OHSS onset, arterial thromboses are less common and occur concurrently with the onset of OHSS. Arterial thromboses are predominately manifested by cerebrovascular accidents.[6]

The diagnosis of mild OHSS is typically made by a history of ovarian stimulation, followed by typical symptoms of abdominal distension, nausea and vomiting.[7] OHSS is further characterized by enlargement of the ovaries, as seen in this case review, with an acute fluid shift. This results in ascites, pleural effusion and generalized edema.[1] In a review of 2,902 patients with OHSS, 209 were found to have severe OHSS. Severe cases are defined as ovarian enlargement >10 cm, massive ascites, pleural effusion, oliguria, liver dysfunction or hemoconcentration >45%.[2, 3, 4] Critical OHSS is classified by thromboembolism or acute respiratory distress syndrome on top of severe symptoms.[7] Of those with severe OHSS, dyspnea was the most common finding in 92% of patients, with pulmonary embolus (PE) found in 2%.[3] Women that appear to be at the greatest risk for OHSS with thromboembolic complications are those with a personal or family history of thromboembolic disease, and those in whom pregnancy is achieved.[8] Compared with patients who develop arterial thrombosis following ART, those who develop venous thromboembolism are more likely to be pregnant. The increased endogenous hCG associated with a pregnant state increases the hypercoagulability of the patient that is already initially hypercoagulable due to ovarian stimulation.[6]

A high index of suspicion must be maintained to recognize thromboembolic events associated with OHSS. If a woman conceives and is diagnosed with OHSS, prolonged monitoring should occur. However, if she does not conceive, resolution of OHSS should occur by the time of her next withdrawal bleed.[7] Outpatient management is appropriate for mild OHSS. Patients should remain hydrated with no less than one liter of

fluid per day to keep urine output adequate (20-40 cc/hour) and to prevent hemoconcentration. Hospitalization is necessary for severe OHSS if the patient has intractable abdominal pain, oliguria, ascites, dyspnea or electrolyte imbalance.[2]

Pain control is the initial treatment when a patient is symptomatic with OHSS. This can be achieved with opiate medications when pain is severe. Nonsteroidal anti-inflammatory agents should be avoided because they can compromise renal function. Nausea usually occurs secondary to ascites accumulation and therefore an effort should be made to reduce abdominal distention. Paracentesis should be considered in severe distention or ascites with colloid replacement. Promethazine can be used safely in pregnant patients for nausea.[7]

Studies indicate that empiric prophylactic unfractionated heparin or LMW heparin should be used in all patients found to have severe OHSS, regardless of evidence for or against thromboembolic disease.[3] Routine screening and treatment for hypercoagulable state is not required at this time with ovulation induction or ART. However, such monitoring may be cost-effective in patients with personal or family history of thromboses. Anticoagulation should always be started if thromboembolism is suspected.[7] A review of 96 cases of thromboses related to OHSS stated that thromboprophylaxis should be considered for all patients with moderate to severe OHSS for 1-2 months beyond the clinical resolution.[6] There is strong consensus that all women that are hospitalized with OHSS should also receive thromboprophylaxis while in the hospital.[2] Furthermore, there is strong consensus that all OHSS patients with evidence of thromboembolic disease should be treated with full heparinization throughout their entire pregnancy, while other studies have suggested that patients be treated for a minimum of 6 months.[3] Evidence also states that no further investigation or treatment for pulmonary thromboembolic events is required postpartum in these patients beyond the 6 month total treatment period.[3]

Conclusions

From both this case report and relevant studies, it is in the best interest of patients undergoing ovulation induction and ovarian stimulation if physicians have a high index of suspicion for complications. Ovarian hyperstimulation syndrome (OHSS) is iatrogenic and serious complications are preventable. In the case of thromboembolism related to OHSS in a pregnant patient, the patient should be fully heparinized for a minimum of 6 months, and often for the remainder of their pregnancy. There is currently no indication to terminate a pregnancy that results in OHSS.

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