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CASE REPORT
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SEVERE OVARIAN HYPERSTIMULATION SYNDROME (OHSS) – LEADING TO AN INTENSIVE CARE UNIT (ICU) ADMISSION AND NEAR-MISS! SUGGESTED ALGORITHM OF MANAGEMENT WITH CASE REPORT.

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ABSTRACT
Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication of ovulation induction. It is characterized by multifollicular, theca-lutein ovarian cysts and an acute shift in body fluid distribution resulting in ascites and pleural and pericardial effusions. Polycystic ovarian syndrome or PCOS is one of the major risk factors for the development of OHSS. We report a case of a 35 year old PCOS patient who was undergoing ovulation stimulation in an IVF (in-vitro fertilization) cycle. 72 hours after egg retrieval, the patient presented to the outpatient department with chief complaints of abdominal pain, nausea, and vomiting. She was admitted for observation and two days later she started complaining of shortness of breath and was found to have developed bilateral pleural effusion and massive ascites. Provisional diagnosis of severe OHSS was made and patient was shifted to ICU for monitoring and started on supportive treatment. She was very hypovolemic and hyponatremic. She was managed with fluid management to maintain intravascular compartment, pain relief, thromboprophylaxis and supportive care and OHSS resolved after one week. In conclusion, although severe complications like pleural effusion are rarely seen in OHSS, prompt diagnosis and successful management is likely to avoid the rapid development of serious life threatening complications.

Keywords: OHSS, PCOS, ICU, Pleural Effusion.

INTRODUCTION
OHSS is an iatrogenic complication of ovulation induction and ovulation stimulation for assisted reproductive techniques (ART) [1-2] and is characterized by cystic enlargement of theovaries and rapid fluid shift from the intravascular compartment to the 3rd space. It is second only to multiple gestation as the most common complication of ART. The incidence of OHSS has been estimated at 20 to 33% for mild cases, 3 to 6% for moderate cases add 0.1 to 2% for severe cases [3-5]. The exact aetiology for the pathogenesis is still unknown but the syndrome is known to be dependent on human chorionic gonadotrophin (hCG), hence most cases are iatrogenic, following gonadotropin

stimulation. The ovaries which are stimulated with gonadotropins and subsequently exposed to HCG lead to the release of vasoactive mediators like vascular endothelial growth factors (VEGF), histamine serotonin, prostaglandins, prolactin, renin-angiotensin system (RAS) from the hyper stimulatory ovaries and hence the pathophysiology of increased vascular permeability [5] causing extravasation of protein rich fluid into the 3rd space. haemoconcentration, electrolyte imbalance, decreased renal perfusion and oliguria, ascites, pericardial effusions and thrombosis which may precipitate significant morbidity and mortality. Ovarian enlargement causes abdominal pain, nausea, and vomiting. Very rarely, OHSS can occur spontaneously due to mutations in follicle-stimulating hormone receptor leading to stimulation of the FSH receptor by chorionic gonadotropin in early pregnancy. The diagnosis of OHSS is made on clinical grounds. Patients commonly present with abdominal distension and discomfort following use of ovulatory stimulation drugs and trigger injection prior to egg retrieval. Depending on the time of occurrence of symptoms, OHSS can be early or late OHSS. Early OHSS (related to excessive preovulatory response to stimulation) presents 3 to 7 days after the hCG trigger whereas late OHSS (related to the occurrence of pregnancy) occurs 12 to 17 days after hCG, is more likely to be severe than the early form. Several schemes have been developed for classifying OHSS based on severity [6] .RCOG,2016 (Green-Top Guidelines) classifies OHSS as mild, moderate, severe, and critical based on clinical, laboratory and hemodynamic parameters (Table 1). As per these parameters,our patient fits in the severe OHSS category. The clinical treatment of OHSS depends on its severity, complications, and absence or presence of pregnancy. The treatment involves treatingthe electrolytic imbalance, hemodynamic changes, liver dysfunction, pulmonary manifestations, hypoglobulinemia, presence or absence of fever, thromboembolic events, adnexal torsion, and neurological manifestations [7]. While mild and moderate OHSS can be managed conservatively on an outpatient basis with proper follow-up, severe and critical OHSS requires hospitalization for monitoring and treatment (medical ± surgical). The prevention of OHSS is based on its prediction and early interventions to halt the progression of done.

TABLE 1: - RCOG CLASSIFICATION OF OHSS

CATAGORY	FEATURES
Mild OHSS	Abdominal bloating
	Mild abdominal pain
	Ovarian size usually r < 8c * m ^ 3
Moderate OHSS	- Moderate abdominal pain
	- Nausea vomiting
	- Ultrasound evidence of ascites
	- Ovarian size usually 8 - 12c * m ^ 2
Severe OHSS	- Clinical ascites (= hydrothorax)
	- Oliguria (< 300 ml/day or < 30 ml/hour)
	- Haematocrit > 0.45
	- Hyponatraemia (sodium < 135 mmol/l)
	- Hypo-osmolality (osmolality < 282 mosm/kg)
	- Hyperkalaemia (potassium > 5 mmol/l)
	- Hypoproteinaemia (serum albumin < 35 g/l)
Critical OHSS	- Ovarian size usually > 12 cm^3
	- Tense ascites/large hydrothorax
	- Haematocrit > 0.55
	- White cell count > 25 000/ml
	- Oliguria/anuria
	- Thromboembolism
	- Acute respiratory distress syndrome

CASE PRESENTATION

The patient, 35 year old female, nulligravida, married for 9 years presented to the outpatient department with chief complaints of pain abdomen, nausea and vomiting post ovum retrieval which was done 3 days before. She had a history of irregular cycles for 5 years and was diagnosed as PCOS (WHO I) and was taking tab metformin 500 mg bd for the same for thelast 4 years. She had undergone a hysteroscopic and laparoscopic evaluation with bilateral ovarian drilling for infertility 3 years back. Her AMH was 5ng/ml, prolactin was 11.1, HbA1Cwas 5.1, rest of the investigations were within normal limits. Pre-treatment serum estradiol levels and antral follicular count were not available. She had visited a fertility clinic where shewas counselled for IVF. She underwent an antagonist cycle with hCG trigger and freeze-all. Gonadotropin used was HP-FSH at 300 IU/day. Patient started feeling uneasy with abdominalpain, nausea and vomiting and shortness of breath 2 days after ovum pickup and reported to hospital a day after.

On admission patient was conscious, oriented, but in mild distress because of lower abdominalpain. She was slightly overweight (BMI of around 27.4kg/m^2) with features of hirsutism and aFerriman-Gallway score of 7. She had a pulse rate of 110 beats/min, good volume, BP of 128/90 mmHg, Oxygen saturation of 94% on room air. She was tachypnoeic on lying down with a respiratory rate of 20/min. Physical examination revealed normal cardiorespiratory examination with a slightly distended abdomen, non-tender to touch. Her haematocrit on admission was 43, abdominal girth was 112cm, serum albumin 1.3g/dl, TLC of 18K/uL, restof the investigations including serum electrolytes were within normal limits. Ultrasonographic examination revealed bilateral bulky ovaries with multiple cysts with right ovarian volume of 120 cc and left ovarian volume of 180cc. There was mild ascites and no other abnormality and no pleural effusion.

Patient was admitted in high dependency unit for observation and was monitored for vitals (oxygen saturation, pulse rate, BP) 4-6 hourly, daily weight and abdominal girth, daily biochemical investigations, daily fluid intake and output and alternate day ultrasonographic monitoring for ascites, presence, or absence of pleural or pericardial effusions and bilateral ovarian volume. Patient was advised to take fluids orally as per thirst and started on the following treatment: -

A) Tab rabeperazole with ondansetron (20/4) BD
B) Tab cabergoline 0.5 mg bedtime
C) Inj.Albumin 20% iv daily.
D) Inj. Enoxaparin 0.6 microgram S/C OD
E) Tab paracetomol 500mg tds for pain relief.
F) Tab metformin 500 mg BD

On day second of admission, patient complained of worsening of abdominal pain and shortness of breath. On examination, oxygen saturation had dropped 86% on room air with decreased air entry in bilateral basal areas of lungs, abdominal girth had increased to 118 cm, there was weight gain of more than 2 kgs in 24 hours. An emergency sonography was done which showed moderate ascites with bilateral pleural effusions of 21 mm and 19 mm on right and left side respectively. Patient was shifted to ICU for further monitoring and management. In the ICU, the patient remained conscious, oriented, however, she required oxygen supplementation in propped up position. She continued with the treatment advised and was monitored carefully daily. Investigations with daily examination report of patient are shown [tables 2-4].

5-6days after starting the treatment, the patient started reporting gradual improvement of symptoms. Hemodynamic and laboratory parameters improved. Sonographically, ascites and pleural effusions regressed, and bilateral ovarian volume decreased. She was discharged on day 12 of admission.

TABLE 2:- BIOCHEMICAL INVESTIGATIONS							
PARAMETERS							
Complete Blood Count	DAY1	DAY2	DAY3	DAY4	DAY5	DAY6	DISCHARGE
Hemoglobin Standard range (13.5-18.0g/dl)	10.2	10	10.3	9.5	9	8.6	8.4
White blood cell count (4.0-11.0 K/uL)	18	17.9	12.7	7	5.5	5.5	5.5
Platelets (150-400 K/uL)	414	349	336	252	239	262	254
Hematocrit (40.0-52.0 %)	43	36.4	30	27	26.3	24.9	30
Liver Function Test							
Serum Bilirubin (0.2-1.0 mg/dl)	0.4	0.3	0.4	0.3	0.2	0.2	0.2
Serum Albumin (3.4-5.0 mg/dl)	1.4	2.6	2.8	3.0	3.2	3.6	3.8
Total protein (6.4-8.2 mg/dl)	4.8	5.2	5.0	5.1	5.6	6.0	6.5
Aspartate Transaminase(AST) (12-40 U/L)	28	26	30	22	38	44	42
AlanineTransaminase(ALT) (15-65 U/L)	33	43	54	44	36	50	55
Alkaline Phosphatase(ALP)(50-135 U/L)	146	312	224	126	158	200	250
Renal Function Tests							
Urea (20-40mg/dl)	21	22	26	30	28	22	24
Creatinine (0.5-1 mg/dl)	0.5	0.5	0.6	0.6	0.5	0.4	0.3
Serum electrolytes							
S.Sodium (135-145 meq/l)	136	132	137	141	146	138	136
S.Potassium (3.5-5.5 meq/l)	3.6	4.2	3.6	3.4	3.2	3.5	3.6

TABLE 3:- PHYSICAL PARAMETERS							
PARAMETERS							
	DAY 1	DAY 2	DAY3	DAY4	DAY5	DAY6	DISCHARGE
WEIGHT (KG)	90.5	92.5	92	90.5	90	89.5	88
ABDOMINAL GIRTH (cm)	112	115	117	115	113	110	108
INPUT/OUTPUT(Litres)	1.2/1.1	1.5/1.3	1.5/2	3/2.5	3/2.7	3.5/3.3	2.2/2

TABLE 4:- USG PARAMETERS						
	DAY 1	DAY 3	DAY 5	DAY 7	DAY9	DISCHARGE
ASCITES	MODERATE	MODERAT E	MODERATE	MILD	MILD	MILD
OVARIAN	R 120 cc	R 280 cc	R 480 cc	R 480	R 320	R 160 cc

VOLUME	L 180 cc	L 340 cc	L 350 cc	cc L 350 cc	cc L 200 cc	L 120 cc
PLEURAL EFFUSION(maximum column depth)	MINIMAL	R 21ccL 19cc	R 25ccL 27 cc	R 27 cc L 23 cc	R 16 L 11	NIL

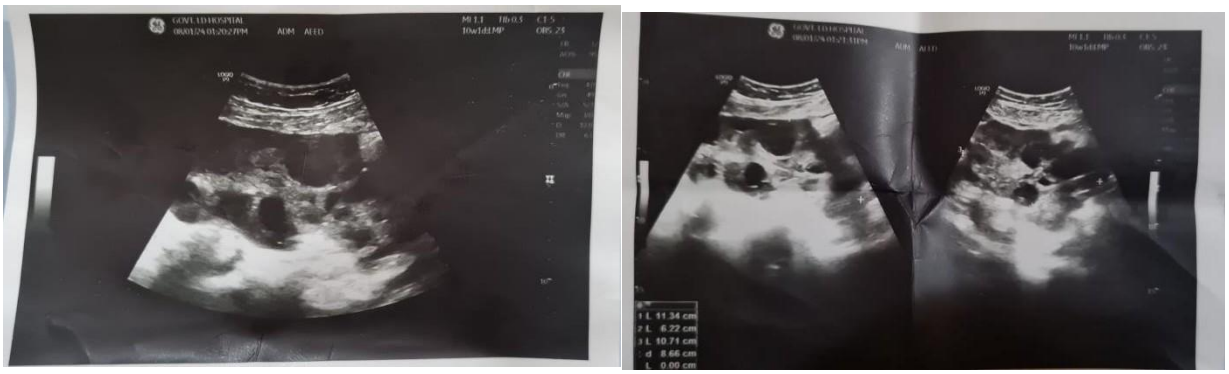

Fig 1 USG picture of bilateral, multi-follicular, enlarged ovaries.

DISCUSSION

OHSS is the most feared complication of ovulation induction. It is characterized by bilateral cystic enlargement and third space fluid shift resulting in ascites, pleural and pericardialeffusion and ovarian neoangiogenesis. The disease can be potentially life-threatening in its severe form, resulting in hospitalization in 1.9% cases [8]. Human chorionic gonadotropin (hCG), either exogenous or endogenous, is the triggering factor for the syndrome.hCG stimulates a high number of granulosa-lutein cells leading to the increased production of vascular endothelial growth factor (VEGF) and other mediators from these cells resulting in a cascade of events which result in increased vascular permeability and hence hypovolemia, oliguria, electrolyte imbalance, ascites, hypercoagulability, pleural or pericardial effusionswhich can cause fatal morbidities and mortalities. The duration of OHSS is longer and its expression is more severe when pregnancy ensues (Late OHSS), especially when there are multiple concepti [7]. Fortunately, the patient in our case report presented with early OHSS. Prediction of OHSS is the cornerstone of prevention. Prediction is based on identifying the characteristics of the patients who would be high responders. The characteristics of patients at risk has been investigated by three groups of investigators from Belgium, Israel, and Egypt [3,9-10]. The characteristics found to increase the risk of OHSS include younger age, low BMI, previous history of OHSS and most importantly WHO II anovulation – especially polycystic ovarian syndrome. In contrast to this, our patient was in her mid-30s and had a high BMI. She had a history of primary infertility and was a known case of PCOS. Alhilali etal in their study found that the incidence and severity of OHSS increased in PCOS patients especially when they had primary infertility [11]. Papanikolaou, Pozzobon [12] (proposed that the high cohort of larger follicles (medium/large follicles > 13 follicles; > 11mm in diameter) is the threshold of OHSS risk with a sensitivity of 84.9% and specificity of 69% . Costello, chew [13] suggested an altered folliculogenenis as one of the main characteristics of polycystic ovaries causing raised LH levels which in-turn increases VEGF bioactivity. Serum anti-Müllerianhormone (AMH), antral follicular count (AFC), pre-treatment serum estradiol levels maypredict the risk of OHSS. Lee and colleagues [14] suggested that an AMH level >3.36 ng/mL was able to predict the development of OHSS (sensitivity=90.5% and specificity=81.3%).

In 2012, Jayaprakasan et al.[15] reported that an AFC≥24 correlated with an increased risk of moderate to severe OHSS. A rapid rise in estradiol levels and serum estradiol concentrations >2500 pg/mL are important predictive factors of OHSS during ovarian stimulation [7-9]. The patient in our case report had a AMH of 5.1 ng/ml which was on higher side while as records of pre-treatment AFC and serum estradiol levels were not available with the patient. As per latest ASRM(American Society for Reproductive Medicine) guidelines (2016), the following points address several aspects of ovarian hyperstimulation syndrome (OHSS) risk, prevention, and management in women receiving assisted reproductive technology (ART) treatments: -

- Women with PCOS, elevated AMH values, and elevated AFC may benefit fromovarian stimulation protocols that reduce the risk of OHSS. Ovarian stimulation protocols using GnRH antagonists are preferable in such patients who are at high risk of OHSS. (Grade A). The patient in our case had received a GnRH antagonist cycle along with an hCG trigger.
- GnRH agonists are recommended to reduce the risk of OHSS if peak estradiol levels are high or multifollicular development occurs during stimulation. (Grade A). Lowdose hCG trigger, luteal hormonal support, or cryopreservation of embryos are strategies that may improve pregnancy rates in this setting. (Grade B)
- The use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval is Dopamine agonist administration starting at the time of hCG trigger for several days also may be used to reduce the incidence of OHSS. (Grade A)
- Additional strategies to prevent OHSS which may be helpful include the use of metformin in PCOS patients (Grade A), aspirin administration (Grade A), and cryopreservation of embryos with low dose hCG co-trigger may increase pregnancy rates without raising the risk of OHSS. (Grade B).
- There is insufficient evidence to recommend coasting or prophylactic albumin administration for the prevention of OHSS. (Grade C).

The management depends on the severity of OHSS and guides the clinician whether admissionis required, or the patient can be managed on an outpatient basis. Attention should be given to correction of the circulatory and electrolyte imbalance and preservation of adequate renal perfusion. The hospitalized patient should be regularly assessed with documentation of vital signs, together with daily weight and girth measurement. Strict fluid balance recording of input-output, daily blood counts with hematocrit, electrolytes, renal and liver function tests is required. The treatment is usually symptomatic until the condition resolves spontaneously.

Fluid replacement (mainly orally, guided by thirst) or intravenous fluid therapy if patient is unable to take orally because of nausea and vomiting, is an important part of treatment. Intravenous crystalloids should be given in cases of persistent hemoconcentration or oliguria. Albumin interrupts the progression of the disease by increasing the plasma oncotic pressure and by binding to some of the vasoactive mediators. Dextran, mannitol, fresh frozen plasma, and hydroxyethyl starch (HAES) can also be used. Abramov et al [16].compared the efficacyof HAES and human albumin and observed HAES to be better than albumin (patients who received HES had higher urine output, needed fewer abdominal paracenteses and pleural thoracocenteses, and had a shorter hospital stay than those who received human albumin). No difference in adverse effects was reported. Recent evidence also demonstrates that the administration of a dopamine agonist, such as cabergoline or guinagolide, from the day ofhCG trigger can reduce the incidence of OHSS by inhibiting the phosphorylation of VEGFR-2in response to hCG [17]. Recent evidence also demonstrates that the administration of a dopamine agonist, such as cabergoline or guinagolide, from the day of hCG trigger can reduce the incidence of OHSS by inhibiting the phosphorylation of VEGFR-2 in response to hCG andassociated vascular permeability and hence interferes with the progression of OHSS [18]. OHSS is a hypercoagulable state and prophylactic treatment with low molecular weight heparin (LMWH) should be instituted. The duration of anticoagulant administration is debatable and should be individualized depending on the patient's risk factors. Antibiotics can be used to prevent hospital acquired infections from iv lines and urinary catheters. Tense ascites with oliguria or deteriorating renal function and

respiratory compromise because of either massive ascites or pleural effusion or pulmonary edema requires an image guided abdominal paracentesis and/or a pleural tap. Morris et.al [19]. in a cohort study of 18 women with severe OHSS, concluded that outpatient ultrasound-guided paracentesis is a safe alternative to hospitalization in patients with severe OHSS. However, our patient responded to the therapy well and did not require any removal of pleural or ascitic fluid.

BASED ON THE PUBLISHED DATA, WE SUGGEST THE FOLLOWING ALGORITHMS FOR THE INPATIENT MANAGEMENT OF A PATIENT WITH OHSS IN TABLE 5-6

TABLE 5
• MONITOR VITAL SIGNS EVERY 2-4 HOURLY, ACCORDING TO CLINICALSTATUS.
• DAILY MONITORING OF FLUID INTAKE AND OUTPUT.
COMPLETE PHYSICAL EXAMINATION INCLUDING
• CHEST AUSCULTATION
• ABDOMINAL GIRTH MONITORING
• DAILY WEIGHT MEASUREMENT
LABORATORY INVESTIGATIONS INCLUDING
• PREGNANCY TEST BIOCHEMICAL MONITERING INCLUDING SERUM ELECTROLYTES RENAN AND LIVER FUNCTION TESTS, AND BLOOD COUNT WITH HIMATOCRIT. EVALUATION OF BLOOD GASES AND ACID-BASED BALANCE
RADIOLOGICAL IIMAGING INCLUDING
• CHEST X-RAY AND ECHO WHEN PLEURAL OR PERICARDIAL EFFUSION IS SUSPECTED.REPEAT IF NECESSARY.
• USG EVALUATION FOR QUANTIFICATION OF ASCITIC FLUID VOLUME,PLEURAL EFFUSION AND BILATERAL OVARIAN SIZE/VOLUME

TABLE 6	
• CORRECTION OF THE CIRCULATORY VOLUME.FLUID,REPLACEMENT BY THE ORAL ROUTE, GUIDED BY THIRST. • INTRAVENOUS FLUIDS INCLUDING IV CRYSTALLOID FLUIDS AT 125-150 ML/HOUR, IFNEEDED	• ELECTROLYTE CORRECTION IFNEEDED. • DIURETICS SHOULD BE AVOIDED AS THEY FURTHER DEPLETE INTRAVASCULAR VOLUME.
• ATHROMBOPROPHYLAXIS WITH LOW MOLECULAR WEIGHT HEPARIN(LMWH). DURATION OF TREATMENT TO BE INDIVIDUALIZED AS PER PATIENT RISK FACTORS.	• ANTIBIOTIC TREATMENT TO PREVENT ANY INFECTION FROM IV LINES AND URINARY CATHETERS AND FOR PREVENTION OF PERITONITIS
• DOPAMINE IN PATIENTS OF OLIGURIA WITH SEVERE OHSS. • CABERGOLINE 0.25 MICROGRAM PER DAY STARTING FROM THE DAY OF ADMISSION.	• SURGICAL TREATMENT IN CASE OF SUSPICION OF OVARIAN TORTION OR RUPTURE. ABDOMINAL OR PLEAURAL CENTESIS IF NEEDED.

CONCLUSION

With the current increase in the availability and use of different fertility treatments and in vitro fertilization, the incidence of OHSS has increased. There is no method that can completely abolish OHSS. However, its prevention can be lifesaving and is principally preferred over its treatment. The disease is usually self- limiting but in rare cases can cause fatal complications such as pleural and pericardial effusions. Early detection and prevention methods may help in identifying and treating

OHSS. Even after the commencement of ovulation induction, it is possible to prevent severe OHSS in almost all patients by careful monitoring, early prediction of an ongoing ovarian hyper-responsiveness, and utilization of appropriate management strategies.

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