10.5005/jp-journals-10016-1065
REVIEW ARTICLE

# Ovarian Hyperstimulation Syndrome

Nalini Mahajan

## ABSTRACT

ART is proven of great help to all the infertile couples anxious to get pregnant , but is not free of side effects and complications. OHSS one of the most important complication especially in cases of PCOS. Ovarian hyperstimulation syndrome (OHSS) is a potentially fatal complication of ovarian stimulation. The incidence has been estimated at 3 to 6% for moderate and 0.1 to 2% for severe OHSS. The trigger for initiation of OHSS appears to be human chorionic gonadotropin (hCG). In conception cycles symptoms may persist longer due to endogenous hCG stimulus .Vascular endothelial growth factor (VEGF), a member of the transforming growth factor superfamily, has emerged as one of the factors most likely involved in the pathophysiology of OHSS. There are various risk factors which increases the risk of developing OHSS during the stimulation like PCOS, low body weight, previous history of OHSS, etc. Primary and secondary preventive measures are been tried to reduce the risk of developing OHSS. GnRHa trigger in patients at risk revealed that incidence OHSS was reduced or totally eliminated. Use of antagonist cycle with an agonist trigger and elective vitrification of all embryos allows us to aim for an 'OHSS Free' clinic today.

**Keywords:** Ovarian hyperstimulation syndrome, Polycystic ovarian syndrome, Vascular endothelial growth factor, Antagonist, human chronic gonadotropin, Gonadotropin-releasing hormone agonist.

**How to cite this article:** Mahajan N. Ovarian Hyperstimulation Syndrome. Int J Infertility Fetal Med 2013;4(3):71-78.

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a potentially fatal complication of ovarian stimulation.[1] OHSS is characterized by cystic enlargement of the ovaries and transudation of fluid and proteins from the intravascular compartment into the third space due to increased capillary permeability. The incidence has been estimated at 3 to 6% for moderate and 0.1 to 2% for severe OHSS.[2]

It is mainly associated with the multifollicular response encountered in gonadotropin stimulations but can occur with use of clomiphene citrate and gonadotropin releasing hormone (GnRH). Spontaneous OHSS[3] occurring in natural conception is rare, but cases have been reported. The trigger for initiation of OHSS appears to be human chorionic gonadotropin (hCG). OHSS is generally a self-limiting disorder and usually resolves spontaneously within 7 to 10 days. In conception cycles symptoms may persist longer due to endogenous hCG stimulus. The clinical presentation can vary from mild to severe life-threatening symptoms requiring hospital admission in 1.9% of cases.[4]

## PATHOPHYSIOLOGY

The pathophysiology of this condition is still not completely elucidated but it is believed to be mediated by an excessive secretion of vasoactive peptides and steroids from the hyperstimulated corpora lutea. Increased follicular fluid levels of prorenin and renin and angiotensin-mediated changes in capillary permeability have been implicated as contributory factors.[5]

Vascular endothelial growth factor (VEGF), a member of the transforming growth factor-β (TGF-β) superfamily, also known as vascular permeability factor, has emerged as one of the factors most likely involved in the pathophysiology of OHSS.[6] An angiogenic cytokine, it is known to stimulate the vascular endothelium and plays an integral role in follicular growth and ovarian angiogenesis.

It has been well-established that the trigger for OHSS is hCG which appears to acts via VEGF. VEGF increases vascular permeability by interacting with its VEGF receptor 2 (VEGFR-2) allowing egress of protein rich fluid (Fig. 1). An increase in VEGF mRNA levels after hCG stimulation points to the fact that hCG stimulates VEGF expression in granulosa cells.[7] Blood levels of VEGF also correlate with the severity of OHSS.

Other factors like angiotensin II, insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), TGF-α and -β, basic fibroblast growth factor (BFGF), platelet-derived growth factor (PDGF), interleukin-1b (IL-1b) and IL-6 may also play a part in the pathogenesis either directly or via VEGF.[5]

Receptor mutation and genetic predisposition also appear to be important pathogenetic factors. Spontaneous OHSS has been reported to develop between 8 and 14 weeks of


**Fig. 1:** VEGF stimulates angiogenesis and vascular hyperpermeability by interacting with its VEGF-2

*Date of Received: 06-04-2013*
*Date of Acceptance: 20-05-2013*
*Date of Publication: September 2013*

amenorrhea in multiple pregnancies, molar pregnancies, pregnant women affected by hypothyroidism, polycystic ovary syndrome (PCOS), gonadotropin-producing pituitary adenoma and also in normal pregnancies. Mutations of FSH receptors have been implicated as a cause for spontaneous OHSS.[8] Di Carlo et al in 2012[9] reported a case of spontaneous, familial, recurrent OHSS in a 26-year-old primipara whose first-degree cousin, paternal grandmother and a number of other members of her father's family had suffered from a similar condition which points to a genetic predisposition.

## CLINICAL PRESENTATION AND CLASSIFICATION OF OHSS

Two forms of OHSS are described based on the onset of symptoms. Early OHSS occurs 2 to 3 days after oocyte retrieval (OR) as a result of the initial hCG trigger. Late OHSS occurs after 10 days of OR/7 days after ET in response to endogenous hCG secretion subsequent to successful implantation.[10] It can also be the result of hCG used for luteal support.

Patient can present with lower abdominal pain, mild distension, nausea, vomiting or diarrhea in mild cases. With progression of disease accumulation of fluid in the abdomen leads to further distension and eventually tense ascites. Nausea and vomiting increase, there is increasing tachypnea and decreased urinary output. Weight gain can be rapid, >1 kg/day. Ultrasound examination shows enlarged ovaries and presence of ascites. Blood tests show hemoconcentration, elevated leukocytes, altered liver enzymes, electrolyte imbalance (hyperkalemia and hyponatremia) and in extreme cases increased creatinine levels. In severe OHSS, fluid can be seen in the pleural and pericardial cavities, leading to intense respiratory discomfort and hypovolemia. Life-threatening complications include hepatorenal failure, acute respiratory distress syndrome, hemorrhage from ovarian rupture and thromboembolism.[11]

Extravasation of protein-rich fluid and contraction of the vascular volume leads to hypotension, which in turn leads to reduced renal perfusion resulting in oliguria and anuria. Tense ascites elevates the diaphragm causing pulmonary compromise which is further aggravated by hydrothorax. Hemoconcentration and decreased peripheral blood flow increases the risk of thromboembolism.

Traditionally two classification have been used; Golan's classification 1989 and that proposed by Rizk and Aboulghar in 1999. A recent classification more objectively related to symptoms than previous classifications (Table 1) incorporates vaginal ultrasound and laboratory parameters.[12] Mild, moderate and severe forms are distinguished by the extent of fluid shift into body cavities. Moderate OHSS involves fluid shifts of less than 500 ml. Severe OHSS involves presence of hemoconcentration and hypovolemia and an alteration in the laboratory parameters. Since, subjective signs and symptoms such as discomfort, pain, nausea, and vomiting, vary in individual cases they have not been assigned to a particular grade of OHSS.

## IDENTIFYING THE PATIENT AT RISK

Identification of risk factors is critical for prevention of OHSS as corrective measures can be taken before the onset of full blown disease. Predictive factors for OHSS can be divided into:

*Primary risk factors:* Inherently present or identifiable before stimulation.

*Secondary risk factors:* Which become obvious during ovarian stimulation when patients with no known predisposing factors experience an excessive response to treatment.

### Primary Risk Factors

- Young age
- Low body weight
- PCOS, or isolated PCOS characteristics because of increased number of recruitable follicles
- H/O previous OHSS or increased response to gonadotropin therapy.

Unfortunately there are no tests that can accurately predict OHSS but hormonal and ultrasound markers have been examined as predictors of ovarian response. Anti-

**Table 1:** Proposed new clinical grading system for OHSS (Humaidan et al, 2010)

| | *Mild* | *Moderate* | *Severe* |
|---|---|---|---|
| Objective criteria | | | |
| Fluid in Douglas pouch | ✓ | ✓ | ✓ |
| Fluid around uterus (major pelvis) | | ✓ | ✓ |
| Fluid around intestinal loops | | | ✓ |
| Hematocrit >45% | | ✓[a] | ✓ |
| White blood cells >15,000/mm$^3$ | | ±[a] | ✓ |
| Low urine output <600 ml/24 h | | ±[a] | ✓ |
| Creatinine >1.5 mg/dl | | ±[a] | ± |
| Elevated transaminases | | ±[a] | ± |
| Clotting disorder | | | ±[c] |
| Pleural effusion | | | ±[c] |
| Subjective criteria | | | |
| Abdominal distention | ✓ | ✓ | ✓ |
| Pelvic discomfort | ✓ | ✓ | ✓ |
| Breathing disorder | ±[b] | ±[b] | ✓ |
| Acute pain | ±[b] | ±[b] | ±[b] |
| Nausea/vomiting | ± | ± | ± |
| Ovarian enlargement | ✓ | ✓ | ✓ |
| Pregnancy occurrence | ± | ± | ✓ |

*Note:* The ± sign means may or may not be present.

[a]If two of these are present, consider hospitalization; [b]If present, consider hospitalization; [c]If present, consider intensive care

Mullerian hormone (AMH) and antral follicle count are two such markers that have shown great promise. AMH is expressed in the granulosa cells of preantral and small antral follicles and is a measure of ovarian reserve and a reliable predictor of ovarian response.[13] Lee et al 2008[14] in a study of 262 IVF cycles with 21 cases (8%) of moderate or severe OHSS found that baseline serum AMH levels were significantly correlated with development of OHSS [odds ratio (OR): 1.7856; p = 0.0004]. An AMH cutoff value of 3.36 ng/ml gave a sensitivity of 90.5% and a specificity of 81.3% for prediction of OHSS.

AFC of ≥12 antral follicles 2 to 8 mm in diameter is a diagnostic criteria of PCOS and an AFC of >14 may predict hyper-response to IVF treatment with a sensitivity of 0.82 and a specificity of 0.89.[15]

### Secondary Risk Factors

Factors which become apparent during stimulation include:

- Absolute levels of E2 ≥ 3,000 pg/ml or rate of increase of serum E2
- Follicular size and number (≥20) on both ovaries
- Number of oocytes collected.

It has been suggested that a combination of the above parameters may better predict OHSS. However, independently or together their accuracy is limited. Other factors being studied for their predictive ability are VEGF, inhibin B (increased inhibin-B production may prime the follicle to over-respond to hCG) and ILs.

## OHSS PREVENTION

Unfortunately the measures for prevention available so far have not been very effective. Two seminal events changed this–introduction of GnRH antagonist which allowed use of GnRH agonist (GnRHa) as ovulation trigger and the discovery that the dopamine agonist cabergoline could counter the increased vascular permeability by dephosphorylation of the VEGF-2 receptor thus reducing the fluid shift (Fig. 2).[16] Introduction and effectiveness of vitrification as a cryopreservation technique proved to be an additional boon. Use of antagonist cycle with an agonist trigger and elective vitrification of all embryos allows us to aim for an 'OHSS Free' clinic today.

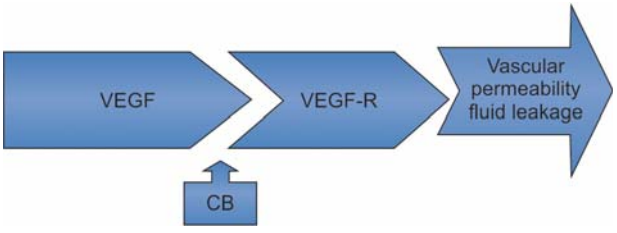


**Fig. 2:** Cb2 acts by dephosphorylation of the VEGF-2

Prevention strategies can be divided into two types—primary and secondary.[12]

*Primary prevention:* Involves using individualized ovarian stimulation protocols based on assessment of ovarian response using AMH, AFC, BMI and age as markers.

*Secondary prevention:* Methods are used to avoid progression to OHSS during stimulation.

### Primary Prevention

1. *Reducing dose of gonadotropin:* Use of individualized stimulation protocols based on assessment of ovarian reserve and response in ART cycles, administration of chronic low dose protocol to promote monofollicular growth in OI cycles and soft stimulation to get 2 to 3 follicles in IUI cycles, aids in OHSS prevention.
2. *Use of GnRH antagonist protocols:* Use of GnRHa in ART protocols lead to higher estradiol levels and an increased incidence of OHSS (4.5% compared with 0.6% for non-GnRHa/hMG cycles).[17] This was largely due to the increased dose of gonadotropins required for stimulation and in some part due to prevention of atresia of smaller antral follicles due to pituitary downregulation.[18]

   The GnRH antagonist protocol has two advantages over agonist, one pituitary suppression is started after stimulation thus, lower doses of gonadotropins can be used and two GnRHa trigger can be used for final oocyte maturation. Cochrane review 2011[19] demonstrated the lower incidence of OHSS with GnRH antagonist (29 trials: OR: 0.43; 95% CI: 0.33-0.57, p < 0.00001). There was no evidence of a statistically significant difference in rates of live-births (OR: 0.86, 95% CI: 0.69-1.08) or ongoing pregnancy (OR: 0.87, 95% CI: 0.7-1.00). Severity of OHSS is also reduced with hospital admissions being significantly lower (OR: 0.46; 95% CI: 0.26-0.82; p = 0.01).
3. *Avoid hCG for luteal phase support:* Luteal phase support is essential in ART as the supraphysiological steroid levels (E2 and P) leads to a negative feedback on the pituitary resulting in early luteolysis with reduced IR, PR's and an increased early pregnancy loss. Luteal support is given with progesterone and frequently hCG. Addition of hCG increases the risk of developing OHSS. Progesterone alone can be used without compromising results.[20]
4. *In vitro maturation:* IVM has been promoted for patients with PCOS, however the technical skill required coupled with lower PRs (10%) in most hands has limited its use. Some centers have reported pregnancy rates of between 20 and 54%.

5. *Insulin-sensitizing agents:* Insulin resistance with compensatory hyperinsulinemia is thought to play a role in the ovarian dysfunction and hyperandrogenism associated with PCOS. In 1997 Velazquez et al[21] reported that the insulin-sensitizing agent metformin improved menstrual cyclicity and ovulation by reducing hyperandrogenism. An improvement in local and systemic hormonal and metabolic parameters, ovulation rates, clinical pregnancies and reduction in pregnancy complications were reported thereafter. Most of these claims were refuted by other authors however, it was established that OHSS rate was significantly reduced in PCOS women undergoing ART (pooled OR: 0.27, 95% CI: 0.16-0.47) with use of metformin.[22]

## Secondary Prevention Strategies

1. *Coasting:* Coasting involves withholding gonadotropins for a minimum of 48 to 72 hours with continued administration of GnRHa till the E2 levels decrease, and then giving the hCG trigger. Coasting has been employed since 1980s and is popular with most physicians since it allows continuation of the cycle without compromising pregnancy, implantation or live birth rates. The optimum time to start coasting is when the lead follicle reaches 16 mm in diameter and hCG should be given when E2 level drops below 3,000 pg/ml. It is recommended not to coast for more than 3 days as that leads to a significant drop in implantation and pregnancy rates.[23]

   Coasting may act by diminishing the functioning granulosa cell cohort–stopping gonadotropin leads to atresia of smaller follicles and reduces VEGF protein secretion (1,413 *vs* 3,538 pg/ml, $p < 0.001$) and gene expression (2-fold decrease) in granulosa cells.[24]

   Though coasting may decrease the severity and incidence it does not eliminate the risk of OHSS. Contrary views were presented by the Cochrane database review 2011.[25] Significantly fewer oocytes were retrieved in coasting groups compared with GnRHa (OR: – 2.44, 95% CI: – 4.30 to – 0.58; $p = 0.01$) or no coasting (OR: – 3.92, 95% CI: – 4.47 to – 3.37; $p < 0.0001$). There was no evidence of a difference in the incidence of moderate and severe OHSS (OR: 0.53, 95% CI: 0.23-1.23) between groups and the authors felt they could not recommend coasting above other methods of OHSS prevention. However, this review has come under criticism because of the number and heterogeneity of the studies.

   *Coasting with GnRH antagonist:* Patients at high risk of OHSS (≥20) follicles/ovary and E2 levels ≥3,000 pg/ml on long agonist protocol have been switched from agonist to daily administration of 0.25 mg antagonist for coasting. A total of 75 IU of HMG is continued with the antagonist till E2 levels fall <3,000 pg/ml at which time an hCG trigger is administered. A significantly faster reduction in E2 (36% in 24 hours), more OR, >grade A embryos and shorter time to trigger were found with antagonist coasting. Clinical PR and MRs were similar.[17]
2. *Reduced dose of hCG trigger:* Long half-life of hCG results in a prolonged luteotropic effect which increases the risk of OHSS. This risk is similar for both urinary-derived and recombinant product.

   Lowering the dose of hCG trigger has been promoted as a method of OHSS prevention. A dose of 5,000 IU instead of 10,000 does not compromise oocyte maturity or pregnancy rates. Doses as low as 3,300 IU and even 2,000 IU have been used successfully to trigger ovulation and help in reducing risk of OHSS.[26]

   Unfortunately lowering the dose does not eliminate OHSS Schmidt et al 2004[27] used doses of 5,000 and 3,300 IU based on E2 levels and reported rates of mild OHSS of 8.5 and 6.3%, moderate OHSS of 2.1 and 10.6%, and severe OHSS of 0 and 4.2% respectively.

   With better strategies available for OHSS prevention increasing the risk even if minimally is not justified.
3. *GnRHa trigger:* Administration of a bolus of GnRHa results in a surge of LH and FSH from the pituitary which mimics the natural mid-cycle gonadotropin surge resulting in final oocyte maturation and ovulation. Though this phenomenon has been known for some time agonist trigger could not be used in ART cycles because of the prevalence of GnRHa downregulated cycles. Use of agonist trigger in antagonist protocols in women at risk revealed that OHSS was reduced or totally eliminated with this regime. HCG triggering increased the risk of developing any form of OHSS by 3.79 times and moderate to severe OHSS by 1.35 times compared with agonist trigger.[28] Unfortunately agonist trigger compromises the luteal phase reducing pregnancy rates and increasing miscarriage rates. Live birth rates too are significantly lower. The oocyte quality however is not compromised as is evident from donor cycles, where PRs and LVBs in recipients do not show any reduction.[29]

   Attempts to improve PRs and MRs by supplementing the luteal phase with high doses of estrogen and progesterone did not help. Supplementing the luteal phase additionally with small doses of hCG 500, 1,000, 1,500 given on the day of OR or in luteal phase improved PR but brought back the risk of OHSS. At present there is no consensus on the ideal luteal phase support in agonist triggered cycles.

4. *Triggering with recombinant LH:* Triggering ovulation with recombinant LH has also been considered as a method of OHSS prevention. Recombinant LH trigger closely mimics the natural LH surge. The cost of the drug and the low pregnancy rates achieved do not support use of this agent.
5. *Cryopreservation of all embryos:* Elective cryopreservation of all the embryos prevents the onset of late OHSS and has been used in high risk patients. Embryos are replaced later in a natural or HRT cycle. Initially there were concerns of embryo loss because of freeze-thaw cycle and lower pregnancy rates[12] however, elective embryo cryopreservation and deferred transfer in patients at risk of OHSS does not compromise the cumulative pregnancy rate per patient and also results in a low overall incidence of severe OHSS.[30] With the advent of vitrification there has been a major improvement in the embryo survival and subsequent PR. Cryopreservation alone cannot eliminate OHSS if hCG trigger is given, as the risk of early OHSS remains. A combination of the antagonist protocol with the agonist trigger and elective cryopreservation can effectively eliminate both early and late OHSS.
6. *Dopamine agonists:* Dopamine agonist cabergoline (Cb2) acts by dephosphorylation of the VEGF-2 receptor (Fig. 2) thus reducing vascular permeability. In 2007 Alvarez[16] presented a proof of concept study for the use of cabergoline in OHSS prevention. Using oocyte donors in his study he compared effect of Cb2 to placebo in women at high risk of OHSS. A total of 0.5 mg of cabergoline was given from the day of hCG for 8 days and this lead to a significant reduction in hematocrit, ascites and a 50% reduction in moderate OHSS. The antiangiogenic effect did not compromise PRs. Though Cb2 is effective in reducing the severity it does not eliminate OHSS. Further studies need to be done to compare cabergoline with established treatments such as intravenous albumin and coasting The nonergot-derived dopamine agonist quinagolide is being promoted currently because of reports of valvular disorder with chronic use of Cb2 in Parkinson's disease.
7. *Plasma expanders-intravenous albumin and hydroxyethyl starch:* Albumin administration corrects the osmotic pressure thus improving intravascular volume and reducing effects related to hemoconcentration. It may also bind to the vasoactive agents responsible for development of OHSS and facilitate their removal from the circulation. Though it is an effective agent in management of established OHSS its role in prevention has been questioned.

   Most studies do not support the use of intravenous albumin on the day of OPU as an effective measure of OHSS prevention though a reduction in severity has been suggested.[31] In a meta-analysis by Jee et al 2010 lower pregnancy rates have been reported with its use.[32] There are potential side effects and risk of pulmonary edema in patients with diminished cardiac reserve. Hydroxyethyl starch (HES) solution has been suggested as an alternative to albumin as it is equally effective, cheaper and safer.
8. *Cycle cancellation:* Cycle cancellation and withholding of hCG is one sure method to prevent OHSS however, it is distressing to the patient and the physician and involves a huge financial loss. With better techniques available today this seems to be a bit extreme. It can only be considered in a setting where a long agonist cycle has been used, E2 levels are extremely high and cryopreservation is not available in which case ofcourse the physician should not be doing IVF at all. A word of caution in OI cycles without downregulation; a natural LH surge may still result in ovulation and natural conception hence contraception should be advised.

### Other Strategies

Methyl prednisolone has been used in OHSS prevention the rationale being that glucocorticoids have an inhibitory effect on VEGF gene expression.[33]

*Follicular aspiration:* Follicles from one ovary are aspirated before hCG trigger. This reduces the functional granulosa cells and thereby the VEGF.

These methods cannot be promoted as much better options are available now.

## MANAGEMENT OF OHSS

Management depends on the symptoms and severity of disease. Tense ascites, significant hemoconcentration and oliguria require immediate hospitalization. The ASRM Practice Committee 2008 Guidelines[5] for management are given below.

### Outpatient Management

Treatment usually requires only oral analgesics and antiemetics. Intercourse should be avoided as it may be painful and may increase the risk of ovarian rupture. Education of the patient regarding symptoms and close monitoring for disease progression is very important. Patient should be in touch with the doctor on a daily basis to give information regarding her symptoms.

Monitoring involves ultrasound examination for assessment of ascites and ovarian size, measurement of

weight and abdominal girth, assessment of urinary output, estimation of hematocrit, liver enzymes, creatinine and electrolytes whenever the clinical situations warrants it.

Recommendations for the outpatient management of persistent and worsening OHSS:

1. Oral fluid intake should be maintained at no less than 1 L per day; preferably electrolyte supplemented drinks.
2. Strenuous physical activity should be avoided to reduce the risk of ovarian torsion. Light physical activity should be maintained. Strict bed rest is unwarranted and may increase risk of thromboembolism.
3. Weight and frequency and/or volume of urine output to be recorded daily. Weight gain of >2 pounds per day or decreasing urinary frequency should prompt repeated evaluation with ultrasound and laboratory tests.
4. Pregnant patients with OHSS must be monitored very closely because of the risk of progressing to severe disease.

## Hospitalization

Hospitalization may be required based on severity of symptoms, analgesic requirements and social considerations. No one symptom or sign is an absolute indication, but hospitalization should be considered when one or more of the following are present:

1. Severe abdominal pain or peritoneal signs.
2. Intractable nausea and vomiting that prevents ingestion of food and adequate fluids.
3. Severe oliguria or anuria.
4. Tense ascites.
5. Dyspnea or tachypnea.
6. Hypotension (relative to baseline), dizziness or syncope
7. Severe electrolyte imbalance (hyponatremia, hyperkalemia), hemoconcentration, abnormal liver function tests.

Laboratory findings in severe OHSS:

1. Hemoconcentration (hematocrit >45%).
2. Leukocytosis (white blood cell count >15,000).
3. Electrolyte imbalances (hyponatremia: sodium <135 mEq/l; hyperkalemia: potassium >5.0 mEq/l).
4. Elevated liver enzymes.
5. Decreased creatinine clearance (serum creatinine >1.2; creatinine clearance <50 ml/min).

Recommendations for monitoring of hospitalized patients with OHSS:

1. Vital signs (every 2-8 hours, according to clinical status).
2. Weight (recorded daily).
3. Complete physical examination (daily, avoiding bimanual examination of the ovaries due to risk of ovarian rupture).
4. Abdominal circumference (at the navel, recorded daily).
5. Monitoring of fluid intake and output (daily, or more often as needed).
6. Ultrasound examination (ascites, ovarian size), repeated as necessary to guide management or paracentesis.
7. Chest X-ray and echocardiogram (when pleural or pericardial effusion is suspected), repeated as necessary.
8. Pulse oximetry (for patients with symptoms of pulmonary compromise).
9. Laboratory investigations
   a. Complete blood count (daily, or more often as needed to guide fluid management).
   b. Electrolytes (daily).
   c. S-creatinine or creatinine clearance, urine specific gravity, repeated as necessary.
   d. Liver enzymes, repeated as necessary.

If a patients complaints of increasing abdominal pain and distension do not forget to look for evidence of ovarian rupture or acute intra-abdominal hemorrhage.

## Fluid Management

Guidelines for fluid management of hospitalized patients:

1. Strict intake and output charting. Limit oral fluids.
2. Rapid initial hydration may be accomplished with a bolus of IV fluid (500-1,000 ml). Thereafter, fluids should be administered judiciously, in the volumes necessary to maintain adequate urine output (>20-30 ml/h) and reverse hemoconcentration. Five percent dextrose in normal saline (DNS) is preferable to lactated Ringer's solution, given the tendency to hyponatremia. Correction of hypovolemia, hypotension and oliguria has highest priority.
3. Albumin (25%) in doses of 50 to 100 gm, infused over 4 hours and repeated at 4- to 12-hour intervals as necessary, is an effective plasma expander and helps to maintain adequate urine output. Albumin is the preferred plasma expander, although others like HES, mannitol, fresh frozen plasma may be used. Dextran has been associated with development of adult respiratory distress syndrome (ARDS) and is best avoided.
4. Treatment with diuretics (e.g. furosemide, 20 mg IV) may be considered after an adequate intravascular volume has been restored (hematocrit < 38%). Premature or overzealous use of diuretics will increase risk of thromboembolism.
5. Onset of diuresis heralds resolution and intravenous fluids should be strictly curtailed at this point.
6. Hyperkalemia is associated with risk of cardiac dysrhythmias hence ECG should be done and appropriate treatment given. Electrocardiographic manifestations of hyperkalemia (prolonged PR and QRS

intervals, ST segment depression and tall peaked T waves) indicate the need for immediate treatment with calcium gluconate.

### Paracentesis

Ultrasound-guided paracentesis is indicated for patients with ascites that causes pain, compromised pulmonary function (e.g. tachypnea, hypoxia, hydrothorax),[32] or oliguria/anuria that does not improve with appropriate fluid management. A transvaginal or transabdominal approach may be used, under ultrasound guidance. The volume of fluid that should be removed in one sitting is not defined but generally the maximum possible is removed at a gradual pace. Pleural tap may be required if hydrothorax is causing dyspnea.

Where risk of thromboembolism is perceived prophylactic treatment with heparin (5,000 U SC, every 12 hours) should be considered. Low molecular weight heparin can also be given for prophylaxis. Full-length venous support stockings can be advised.

## CONCLUSION

OHSS is a potentially life-threatening complication of gonadotropin stimulation. Overtime there has been an improvement in understanding the pathogenesis of the syndrome. An increased vascular permeability related to increased VEGF secretion is mainly responsible for the signs and symptoms associated with the disease. It is important to look out for the risk factors and adopt preventive measures both prior to and during stimulation.

Identification of risk factors and subsequent usage of individualized gonadotropin dosage in an antagonist protocol should be the rule. If during stimulation the number of small and medium sized follicles are high >15 and/or E2 levels are >3,500 pg/ml then an agonist flare with elective vitrification should be planned. For E2 levels between 3,000 and 3,500 a reduced dose of hCG 5,000 IU is to be used for trigger and Cb2 added from day of hCG if fluid is already present in the pelvis. If for some reason embryo transfer needs to be done then an agonist flare with administration of high estrogen and progesterone support is required. Additionally, a small dose of HCG 1,500 IU at the time of trigger or 500, 1,000 IU in the luteal phase–on day of ET and day 5 after ET can be given. In our unit luteal phase hCG is only given after doing an ultrasound to check for fluid and ovarian size, patient is closely monitored and intravenous HES and Cb2 is administered if there is any evidence of fluid collection after hCG administration. Using this regime we have achieved a near zero OHSS status.

We have come a long way in improving the safety of ART and it is incumbent on the IVF specialist to be well versed with the latest developments to avoid the morbidity and mortality associated with this dreaded complication.

## REFERENCES

1. Cluroe AD, Synek BJ. A fatal case of ovarian hyperstimulation syndrome with cerebral infarction. Pathology 1995 Oct;27(4): 344-346.
2. Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. Hum Reprod Update 2003 May-Jun;9(3):275-289.
3. Francisco C, Júlio C, Pinto G, Martins AT, Ferreira A, Martins L. Ovarian hyperstimulation syndrome in a spontaneous pregnancy. Acta Med Port 2011 Dec;24 (Suppl) 3: 635-638.
4. Mocanu E, Redmond ML, Hennelly B, Collins C, Harrison R. Odds of ovarian hyperstimulation syndrome (OHSS)—time for reassessment. Hum Fertil (Camb) 2007 Sep;10(3):175-181.
5. The Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril 2008 Nov;90(5 Suppl):S188-S193.
6. Koninckx PR, Renaer M, Brosens IA. Origin of peritoneal fluid in women: an ovarian exudation product. Br J Obstet Gynaecol 1980 Mar;87(3):177-183.
7. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J, Simon C. The pathogenesis of ovarian hyperstimulation syndrome: in vivo studies investigating the role of interleukin-1b, interleukin-6, and vascular endothelial growth factor. Fertil Steril 1999 Mar;71(3):482-489.
8. Montanelli L, Delbaere A, Di Carlo C, Nappi C, Smits G, Vassart G, Costagliola S. A mutation in the follicle-stimulating hormone receptor as a cause of familial spontaneous ovarian hyperstimulation syndrome. J Clin Endocrinol Metab 2004 Apr; 89(4):1255-1258.
9. Di Carlo C, Savoia F, Ferrara C, Tommaselli GA, Bifulco G, Nappi C. Case report: a most peculiar family with spontaneous, recurrent ovarian hyperstimulation syndrome. Gynecol Endocrinol 2012 Aug;28(8):649-651.
10. Mathur RS, Akande VA, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril 2000 May;73(5):901-907.
11. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril 2000 May;73(5):883-896.
12. Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril 2010 Jul;94(2):389-400.
13. Gnoth C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of anti-Mullerian hormone measurement in a routine IVF program. Hum Reprod 2008 Mar;23(6): 1359-1365.
14. Lee TH, Liu CH, Huang CC, Wu YL, Shih YT, Ho HN, Yang YS, Lee MS. Serum anti-Mullerian hormone and estradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproduction technology cycles. Hum Reprod 2008 Jan;23(1): 160-167.
15. Kwee J, Elting ME, Schats R, McDonnell J, Lambalk CB. Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization. Reprod Biol Endocrinol 2007;5:9.

16. Alvarez C, Martí-Bonmatí L, Novella-Maestre E, Sanz R, Gómez R, Fernández-Sánchez M, Simón C, Pellicer A. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab 2007 Aug;92(8):2931-2937.
17. Aboulghar M. Antagonist and agonist coast. Fertil Steril 2012 Mar;97(3):523-526.
18. Jayaprakasan K, Hopkisson JF, Campbell BK, Clewes J, Johnson IR, Raine-Fenning NJ. Quantification of the effect of pituitary down-regulation on 3D ultrasound predictors of ovarian response. Hum Reprod 2008 Jul;23(7):1538-1544.
19. Al-Inany HG, Youssef MAFM, Aboulghar M, Broekmans FJ, Sterrenburg MD, Smit JG, Abou-Setta AM. Gonadotropin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev 2011 May;11(5): CD001750.
20. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 2011 Oct 5;(10):CD009154.
21. Velázquez E, Acosta A, Mendoza SG. Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. Obstet Gynecol 1997 Sep;90(3):392-395.
22. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Freitas V. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2009 Apr 15;(2):CD006105.
23. Mansour R, Aboulghar M, Serour G, Amin Y, Abou-Setta AM. Criteria of a successful coasting protocol for the prevention of severe ovarian hyperstimulation syndrome. Hum Reprod 2005 Nov;20(11):3167-3172.
24. Garcia-Velasco JA, Zúñiga A, Pacheco A, Gomez R, Simon C, Remohi J, Pellicer A. Coasting acts through downregulation of VEGF gene expression and protein secretion. Hum Reprod 2004 Jul;19(7):1530-1538.
25. D'Angelo A, Brown J, Amso NN. Coasting (withholding gonadotropins) for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev 2011 Jun 15;(6):CD002811.
26. Kashyap S, Leveille M, Wells G. Low dose hCG reduces the incidence of early and severe ovarian hyperstimulation syndrome. Fertil Steril 2006;86(Suppl 2):S182-S183(P-138).
27. Schmidt DW, Maier DB, Nulsen JC, Benadiva CA. Reducing the dose of human chorionic gonadotropin in high responders does not affect the outcomes of in vitro fertilization. Fertil Steril 2004;82:841-846.
28. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 2008 Jan;89(1):84-91.
29. Bodri D, Guillén JJ, Galindo A, Mataró D, Pujol A, Coll O. Triggering with human chorionic gonadotropin or a gonadotropin-releasing hormone agonist in gonadotropin-releasing hormone antagonist-treated oocyte donor cycles: findings of a large retrospective cohort study. Fertil Steril 2009 Feb;91(2):365-371.
30. Vyjayanthi S, Tang T, Fattah A, Deivanayagam M, Bardis N, Balen AH. Elective cryopreservation of embryos at the pronucleate stage in women at risk of ovarian hyperstimulation syndrome may affect the overall pregnancy rate. Fertil Steril 2006 Dec;86(6):1773-1775.
31. Aboulghar M, Evers JH, Al-Inany H. Intravenous albumin for preventing severe ovarian hyperstimulation syndrome: a Cochrane review. Hum Reprod 2002 Dec;17(12):3027-3032.
32. Jee BC, Suh CS, Kim YB, Kim SH, Choi YM, Kim JG, Moon SY. Administration of intravenous albumin around the time of oocyte retrieval reduces pregnancy rate without preventing ovarian hyperstimulation syndrome: a systematic review and meta-analysis. Gynecol Obstet Invest 2010;70(1):47-54.
33. Nauck M, Karakiulakis G, Perruchoud AP, Papkonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. Eur J Pharmacol 1998 Jan;341(2-3):309-315.

## ABOUT THE AUTHOR

### Nalini Mahajan

Director, Mother and Child Hospital, New Delhi; Clinical Director NOVA IVI Fertility, New Delhi, India, e-mail: nalinimahajan@hotmail.com