Ovarian hyperstimulation syndrome

Jan Gerris¹, Petra De Sutter ²

¹ Centre for Reproductive Medicine, Middleheim Hospital, Lindendreef 1, 2020. Antwerp, Belgium
² Centre for Reproductive Medicine, University of Ghent, De Pintelaan 185,900, Ghent, Belgium

Definition
Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of the luteal phase and/or early pregnancy after ovulation induction (provoking ovulation in anovulatory women) or of ovarian stimulation (in the context of intrauterine insemination or in vitro fertilisation).

Essential characteristics
The essence of the OHSS is cystic enlargement of the ovaries and a fluid shift from the intravascular to the third space due to increased capillary permeability and ovarian neo-angiogenesis. Its occurrence is dependent on the administration of human chorionic gonadotropin (hCG). OHSS is extremely rare without hCG administration. Its impact on the general health of the patient can be very deleterious and fatal cases have occasionally been reported.

Early and late forms of OHSS
The early form of OHSS, although elicited by hCG, is related to an exaggerated ovarian response to gonadotropin stimulation, whereas the late form is mainly related to the secretion of placental hCG. The most recent definition still relies on the underlying etiology but makes a clear distinction between the early form (within days after the ovulation triggering injection of hCG) and the late form (10 days after hCG)¹. Particularly those cases which constitute an early form followed by pregnancy are serious and long-lasting ².

Incidence
Precise figures of incidence are unknown because of lack of systematic registration. Mild ovarian hyperstimulation probably occurs in 8-23% of stimulated cycles, moderate form in <1-7% and severe form in ~0.5% of stimulated cycles ³⁻⁴. This causes severe OHSS to be viewed by individual gynecologists as a relatively rare complication. However, the total annual number in the world is estimated to be in thousands. The incidence has almost surely increased over the years ⁵. There are fatal cases although these are never reported. Given the reason for treatment (infertility in young healthy women), each death is a disaster that should have been avoided.

Clinical picture
Most frequent symptoms and signs are –
- Distention of lower abdomen
- Progressive increase in abdominal circumference measured at the level of the umbilicus
- Ovaries enlarged up to >12 cm
- Nausea and vomiting preventing intake of food and fluids.
- Dyspnea and respiratory distress due to an elevated diaphragm and hydrothorax
- Diarrhea
- Quick weight gain

More severe signs and symptoms are –
- Ascites
- Hypotension
- Pleural effusion (more, and more frequently on the right side)
- Pericardial effusion
- Adult form of respiratory distress syndrome (ARDS)
- Oliguria and anuria
- Multiple organ failure
- Death (1/500,000 cycles) ⁶
**Biological findings are** –

- Electrolyte disorders (hyponatremia <136 mEq/L; hyperkalemia >5.0 mEq/L)
- Hypovolemia
- Hemoconcentration (hematocrit > 45%)
- Leukocytosis >15,000/mm³
- Creatinine clearance < 50 mL minute; serum creatinine >1.2 mg/dL
- Elevated liver enzymes
- Hypercoagulability
- Hypoproteinemia and hypoalbuminemia (< 30g/L)

**Additional complications are** –

- Ovarian torsion
  It causes sudden and extreme abdominal pain, and nausea. Its incidence is 1/5000 stimulation cycles but it is more frequent if OHSS and pregnancy are present 7.

- Ovarian bleeding
  It is due to ovarian rupture or intraovarian bleeding caused by pressure or bimanual examination. It leads to signs of acute hemorrhage (hypotension, nausea, sudden drop in hematocrit).

- Thromboembolism
  Both venous (65.7%) and arterial localizations have been described and 83% of these occur in the veins of neck, arm or head (60%). Thrombosis also occurs in arteries and veins of the lower body 8. Pulmonary embolism occurs in 4 to 12% 8. Embolism has been described in the humeral, subclavian and internal jugular veins and in vena cava, and in subclavian, ulnar, internal carotid, medial cerebral and the coronary arteries.

**Risk factors**

**Primary risk factors are** –

- Polycystic ovarian syndrome (PCOS)
- Patients with some characteristics of PCOS:
  - High number of follicles in both ovaries at the quiescent state before stimulation (10 follicles of 4-10 mm in each ovary)
  - LH/FSH ratio >2
  - Hyperandrogenism
- History of OHSS
- Young patients (less evidence)
- Lean women (less evidence)
- Allergic predisposition (less evidence)

**Secondary risk factors are**

- High serum estradiol >3000-4000 pg/mL
  - No clear cutoff value
  - Relatively poor predictive power (maximum 73%)
  - Estradiol itself is no mediator since OHSS is also possible with low serum estradiol values (stimulation with recFSH)
  - The slope of the estradiol rise is the main risk factor and is of greater importance than the maximum level (positive predictive value 77%)
- Number of follicles per ovary >20-25
  - No clear cutoff value (10-35)
  - Variation dependent upon operator and technic
- Measurements of the absolute vascular endothelial growth factor VEGF serum concentrations are not useful for individual prediction 1.

**Physiopathology**

The physiopathology of OHSS is increasingly better understood. The crux is an equilibrium between pro-angiogenic and antiangiogenic factors present in follicular fluid. The proangiogenic role of the VEGF is beyond doubt the most important mediator of the syndrome 10-11. High concentrations of VEGF have been demonstrated in follicular fluid, making the mediating role of ovarian VEGF in the development of OHSS very plausible. VEGF concentrations in ascitic fluid, serum and plasma in OHSS patients were shown to be increased 12-14. mRNA expression of VEGF in human luteinized granulosa cells is time and dose dependent of hCG, further underlining the role of VEGF in the development of OHSS 15-16. Two VEGF receptors exist (VEGFR-1 and VEGFR-2), both produced by endothelial cells, of which one exists in a soluble form, s(serum)VEGFR-1, acting as a negative modulator of the bioactivity of VEGF.

Excess of bioactive pro-angiogenic VEGF increases the risk for OHSS. Excess of anti-angiogenic sVEGFR-1 (and other anti-angiogenic factors) decreases the ovarian response and the risk for OHSS, and is accompanied by a decreased pregnancy rate 18. Absolute serum concentrations have no value in the individual risk assessment because there are individual variations in the binding of VEGF to its receptors 1,11.

In rats, proof of concept was shown by VEGF-2 inhibitor (SU5416) blocking hCG dependent VEGF production (and ensuing neoangiogenesis) 17. Also in rats it was shown that ovulation triggering using LH instead of hCG results in lower VEGF production. This serves as the theoretical basis for ovulation triggering utilizing rLH in clinical situations 18.
The physiopathological cascade of the OHSS consists of neoangiogenesis and increased capillary permeability of the enlarged ovarian and other endothelial surfaces, fluid shift from the intravascular space to the extravascular space (abdomen, pleura, pericardium), hemoconcentration, decreased renal clearance, oliguria/anuria, hyperviscosity of blood, modification in coagulation factors, and thromboembolic risks. Hemoconcentration leads to an increase in hematocrit, in concentration of platelets and leukocytes, in creatinine, in urea and in liver enzymes in the plasma, and to hyperkalemia and acidosis. Serum albumin decreases as a result of extravasation of fluid and ascites formation. The process is self-limiting as the hCG effect decreases unless fetal hCG begins to be secreted.

Classification

The quantitative aspects of the definition of the syndrome cannot be measured exactly. Ovarian dimensions can be assessed to a certain extent by using sonography, but ascites volume is difficult to measure. Therefore classification is not categorical and daily weighing and fluid balance assessment remain key elements of the clinical follow-up. The most frequently used classification system is the one proposed by Golan (Table 1).

Table 1. Classification of OHSS according to Golan (1989).

<table>
<thead>
<tr>
<th>Grade of OHSS</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Abdominal distention and discomfort</td>
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<tr>
<td>2.</td>
<td>Criteria of grade 1 plus nausea, vomiting, and/or diarrhea. Ovaries enlarged 5-12 cm</td>
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<td>3.</td>
<td>Criteria of mild OHSS plus echographic signs of ascites</td>
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<td>4.</td>
<td>Criteria of moderate OHSS plus clinical signs of ascites and/or hydrothorax and respiratory distress</td>
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<td>5.</td>
<td>All of the above plus changes in blood volume and viscosity, hemoconcentration, coagulation disorders, and decreased renal output and function</td>
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<tr>
<td>6.</td>
<td>Life threatening form</td>
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Subsequently, two further refinements were introduced viz., critical OHSS and group C severe OHSS, both of which describe the same life threatening clinical entity of severe reduction in circulating volume, severe hemoconcentration, multiple organ failure (kidney, liver, heart) and/or thromboembolic symptoms. Both are considered as grade 6 in the modern classification of Golan.

It is essential to understand that these grades are not strictly separated entities and that a mild grade OHSS can quickly evolve into a severe OHSS. This should not be forgotten when deciding to follow-up a patient by telephone. The foremost criterion of clinical seriousness implying immediate hospitalization is a hematocrit > 45%.

Prevention

1. Primary prevention

Patients who have a primary risk for OHSS should be exposed to gonadotropins as little as possible. This implies that all other safer treatments like life style changes (diet and exercise), oral ovulation induction, use of pulsed GnRH, and laparoscopic ovarian drilling should be given fair chances. This should especially be kept in mind when treating young women in their first ART treatment cycles, women with PCOS, and women with a history of OHSS.

Identifying of women with thrombophilia, recording a family history of thromboembolism, and finding women with antiphospholipid antibodies should ideally be done before starting gonadotropin treatment. When indicated, the lowest possible dose of gonadotropins should be used and treatment adequately monitored, which means frequent use of vaginal echography and of serum estradiol measurements. All patients at risk should be informed orally and in writing so that at the occurrence of early symptoms, they should consult the responsible gynecologist and not an inexperienced physician.

In cases of high primary risk, prophylactic treatment with heparin has been proposed.

2. Secondary prevention

a) Cycle cancellation

In ovulation induction, withholding hCG prevents the early form of OHSS. Avoiding hCG and intercourse or insemination prevents both the early and the late form. This decision is often psychologically difficult, especially in IVF, because it may entail the loss of considerable financial efforts in countries with no reimbursement. In very severe cases with poor follow-up possibilities, however, it may be the only method to avoid disaster.

b) Coast ing (“Soft landing”)

i) Principle
When high risk patients rapidly reach high (>3000 pg/mL) serum estradiol levels with a large number (>20 per ovary) of follicles during stimulation, gonadotropin administration can be decreased or stopped while continuing GnRH agonist administration. This allows larger follicles to continue to grow, while intermediary and small follicles enter atresia. Based on the FSH threshold theory, a number of follicles will not respond any longer to the decreasing FSH levels or become unresponsive to hCG. Coasting causes a down regulation of VEGF gene expression and protein production as a result of increased apoptosis in granulosa cells of all but mainly immature follicles but does not influence oocyte quality and endometrial receptivity.

Although no randomized clinical trials have been conducted to assess its true efficiency, the method is very popular and is followed by acceptable pregnancy rates. It has the advantage that the cycle is brought to its expected end with the replacement of fresh embryos and that no additional technical procedures are needed.

### ii) Criteria

Criteria for coasting are based on a relationship between the number of growing follicles and/or the serum estradiol levels and the risk for OHSS. There are two criteria for making decision – the serum E₂ levels determine whether coasting be done or not, and the echographic image determines when.

**Serum estradiol** – Most authors use values between 2500-3000 pg/mL as a criterion. Continuing gonadotropins at a serum estradiol level of >3000 pg/mL is considered not good clinical practice. When using recFSH, estradiol values tend to be lower and the above criterion does not hold. It has therefore been suggested that the estradiol value should come into play only if there are >20 follicles per ovary.

**Number of growing follicles** – Coasting should not be started too early because follicle growth might come to a complete standstill. When >30% of all follicles have reached a mean diameter of 15 mm, coasting will result in an abrupt stop in follicle development and a quick serum E₂ decrease. On the other hand, when the majority of the follicles are >15 mm at the start of coasting, a number of cystically enlarged follicles with decreased oocyte quality may ensue. Hence the rule of the golden middle way is coasting should start when ~50% of the follicles are ~15 mm in diameter and have become independent of further gonadotropin stimulation.

### iii) Duration of coasting

It has been shown that a coasting period of 4 days (from the first day the gonadotropin dose is interrupted or decreased) results in decreased pregnancy rates, but this remains controversial. Further clinical research is desirable to assess the subtleties with respect to oocyte numbers and quality, and endometrial receptivity.

### c) Modification of the ovulation triggering agent

Although good data are lacking, it is not impossible that doses of hCG lower than 5000 or 10,000 IU usually utilized may cause sufficient oocyte maturation while reducing the risk for OHSS. Replacement of hCG by exogenous or endogenous LH as ovulation trigger could have a considerable impact on the incidence of early form of OHSS. An endogenous LH surge can be provoked by the administration of a short-acting GnRH agonist. This is only possible in cycles without pituitary desensitization by a GnRH agonist. Combination with an antagonist remains a possibility. Administration of exogenous LH (recLH) is another option but for the time being there is no interest from the side of the pharmaceutical industry to commercialize this indication for this freely available product. The fact remains that the 50 year old use of urinary hCG as ovulation trigger is much cheaper but the impact on the incidence of OHSS is huge.

### d) Administration of macromolecules

#### i) Albumin administration

Prophylactic albumin administration is supposed to interrupt the development of OHSS by increasing the plasma oncotic pressure and binding mediators of ovarian origin. This effect could be counteracted by increased capillary permeability. Prospective randomized trials and one retrospective study with a control group show 39 cases of OHSS in 468 treated risk cycles (8.3%) vs 89 OHSS cases in 611 untreated risk cycles (14.6%). The Cochrane review also shows that intravenous albumin administration at the time of oocyte collection has a preventive effect in cycles with a severe risk for OHSS. However, a recent prospective randomized trial of 488 cases in each arm of the study seems to prove the inefficiency of human albumin. Two studies show a decreased pregnancy rate after the use of intravenous albumin. Albumin administration also has side effects like viral transmission, nausea, vomiting, and febrile and allergic reactions. Besides albumin is expensive too.

#### ii) Hydroxyethyl starch solution (HEAS)

Because of the risk of viral transmission with human albumin, some authors have tested the effect of this safer non-biological substitute with comparable physiological properties. Three studies suggest a useful effect but the cohorts are too small to draw definite conclusions. Further clinical research seems warranted.

### e) Cryopreservation of all embryos

Instead of canceling the cycle, it is also possible to administer...
hCG to retrieve the oocytes and to freeze all embryos. This does not exclude the risk for the early form of OHSS but it does exclude the late form caused by pregnancy. The removal of a large number of granulosa cells from the follicles probably also decreases the risk. The Cochrane Review concludes that the present evidence is insufficient to consider this approach as the standard of treatment. It may be considered when coasting has not been applied when it should have been and when at the time of oocyte retrieval one finds oneself in a very high risk situation for the early form of OHSS in a patient with a very good prognosis of becoming pregnant and hence having a high risk for the late form of OHSS.

f) Summary

Apart from withholding hCG, still the ubiquitous ovulation triggering agent, no method can prevent all cases of OHSS. Other molecules exist (rLH) but are either not available or are very expensive. In ART practice coasting is still the most popular approach which probably does have some preventive effect. The late form cannot be completely avoided altogether. Combinations of different preventive methods acting at different levels could give the opportunity to completely avoid OHSS. Single embryo transfer after ART prevents multiple pregnancies but not OHSS.

Clinical management

a) Criteria for hospitalization
- Hematocrit >45%
- Any sign of severe OHSS

b) Elements of outpatient follow-up
- Daily fluid balance
- Daily weighing
- Increase in umbilical abdominal circumference
- Instruction to contact the center at any sign of deterioration
- Outpatient follow-up every 48 to 72 hours with blood tests and ultrasound examination

c) Elements of hospitalzation follow-up
- Heart rate
- Blood pressure
- Daily fluid balance
- Echographic assessment, ascitic fluid volume and ovarian dimensions
- Pleural tapping (if dyspneic) to diagnose and drain pleural effusion
- ECG (to exclude pericardiac effusion)

- Hematological examination – hematocrit, complete blood count, electrolytes, kidney function tests, liver enzymes, total serum proteins and albumin, and coagulation tests

d) Treatment strategy

(i) Maintain diuresis

(ii) Fluid management
- Intravenous administration of Ringer lactate solution
- First 24 hours – 1500-3000 mL. In order to avoid over-administration of fluid, some centers restrict total fluid intake (inclusive of oral) to 1500 mL
- Subsequent days – fluid volume to maintain fluid balance
- Combination of Ringer lactate and 5% dextrose solution or normal saline and 5% dextrose solution

(iii) Plasma expanders
- HEAS 6% solution in isotonic NaCl
- Maximal daily dose – 33 mL/kg in 250-500 mL per day by intravenous drip utilizing slow administration to avoid lung congestion

(iv) Albumin administration

Because of the risk for hepatitis, overdosage with albumin, renal function disorders, and high cost it is given only if hypoalbuminemia (<28mg/dL) is demonstrated. It should definitely be started when ascitic fluid is drained because this causes huge protein loss.

e) Anticoagulant drugs

Low molecular weight heparin preparations are preferably given primarily in all cases of severe OHSS with hospitalisation but certainly in the presence of –

- Clinical signs of thromboembolic complications
- Documented thrombophilia
- History of hypercoagulability or thromboembolism
- Uncorrected hemoconcentration after 48 hours of usual intravenous treatment

As a prevention of thromboembolic complications, especially in patients who are immobilized due to obesity or other reasons, low dose aspirin administration has been suggested. When drainage of ascites is performed, this has to be weighed against the risk of bleeding. If available, TED-stockings may be indicated.

f) Drainage of ascites

This can be performed both abdominally and vaginally, but always under sonographic guidance. It is considered
when there is severe abdominal discomfort with dyspnea and it results in quick subjective relief for the patient. It also results in an increase in venous return, cardiac output, diuresis, creatinine clearance and lung ventilation. It should be performed gradually – maximum 4 liters over 12 hours. Removal of large quantities means losing huge amounts of protein which must be substituted. One liter of ascitic fluid contains 3.0-3.5 g of albumin and administration of 30-50 g albumin daily is recommended.

Outpatient management of OHSS can only be performed following strict rules. When signs of deterioration occur, hospitalization should be considered, preferably in a center with necessary expertise. Hospitalized patients must be visited frequently by the same physician as the clinical picture may change quickly, even over the period of a single day, and the clinician can and must recognize this. When critical OHSS exists, the patient must be admitted to an intensive care ward. In very severe cases interruption of a starting pregnancy should be considered.

Pregnancy after OHSS

The pregnancy rate in patients with OHSS is higher than average. This is because the patients usually are young women, in their first ART cycle, with many oocytes and several good quality embryos. Several authors have reported an increase in early pregnancy loss in OHSS patients.

Conclusions and recommendations

Although theoretically well known, OHSS remains underestimated because the perceived incidence per gynecologist is low. The affection is very traumatizing for the patient and her partner. Subjective discomfort is very important and objective changes may be dramatic. Although long term sequela like thromboembolism are rare, they are serious. Though fatal cases are rare, they go unreported and so may be underestimated.

Essential recommendations therefore are –

1. Gonadotropin treatment for ovulation induction only when all other options have failed after a sufficiently long trying time.
2. If gonadotropin stimulation for ovulation induction is unavoidable, one should use “friendly” stimulation regimens aiming at (SOFT) single ovarian follicle viz., low dose step-up regimen, step-down regimen, use of antagonists, and utilization of blood and sonographic control of ovarian response.
3. hCG as an ovulation trigger should be replaced by safer methods like rLH and endogenous GnRH-surge by an agonist. They exist but are not commercially available yet.
4. In IVF/ICSI the principle of obtaining as many oocytes as possible should be replaced by softer stimulation regimens aiming at fewer oocytes of good quality.
5. In risk situations the patient should be informed about possibilities such as cancelling, coasting, and freezing embryos for subsequent replacement.
6. When signs of OHSS occur, the patient must be adequately informed and hospitalization should be proposed at the slightest deterioration.
7. These patients need a hospital ward where the clinical picture is well understood and the personnel have expertise in its treatment and follow-up. Admission to an intensive care unit is necessary when critical OHSS develops.
8. Registration of all cases of severe OHSS and their outcome should become compulsory in all ART programs and also after every ovulation induction.

References


