

Ovarian Hyperstimulation Syndrome
(OHSS)
Guidelines

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1. DESCRIPTION OF THE PROBLEM

1.1 Definition

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

1.2 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 of the administration of human chorionic gonadotropin (HCG). Without HCG, OHSS is extremely rare. Its impact on the general health of the patient may be very important. Fatal cases have occasionally been reported.

1.3 Early and late form 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 (Mathur et al., 2000) still relies on the underlying aetiology but makes a clear distinction between the early form (<10 days after the ovulation triggering injection of HCG) and the late form (≥ 10 days after HCG). Particularly those cases which constitute a combination of the early form and are followed by pregnancy are serious and long-lasting (Papanikolaou et al., 2004).

1. ANALYSIS OF AVAILABLE KNOWLEDGE

2.1 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 forms in <1-7% and severe forms in ~0.5% of stimulated cycles (Golan et al., 1989; Navot et al., 1992). This causes severe OHSS to be viewed by individual gynaecologists as a relatively rare complication. However, the total annual number in the world is estimated to be in the thousands. The incidence has almost surely increased over the years (Abramov et al., 1999). There are fatal cases although these are almost never reported. Given the reason for treatment (infertility in young healthy women), each death is a disaster that should have been avoided.

2.2 Symptoms

Most frequent symptoms and signs

- Low abdominal distension
- Progressive increase in abdominal circumference measured at the level of the umbilicus.
- Ovaries enlarged up to >12cm.

- Nausea and vomiting preventing intake of food and fluids.
- Dyspnoea and respiratory distress due to an elevated diaphragm and hydrothorax.
- Diarrhoea.
- Quick weight gain.

More severe signs and symptoms

- Ascites.
- Hypotension.
- Pleural effusion (more and more frequently at the right side).
- Pericardial effusion.
- Adult form of RDS
- Oliguria and anuria
- Multiple organ failure.
- Death (1/500.000 cycles) (Brinsden et al., 1995)

Biological findings

- Electrolyte disorders (hyponatremia <136 mEq/L; hyperkalemia >5.0 mEq/l).
- Hypovolemia.
- Hemoconcentration (hematocrit >45%).
- Leucocytosis >15.000/mm³
- Creatinin clearance <50ml.min; serum creatinin >1.2mg/dl.
- Elevated liver enzymes.
- Hypercoagulability.
- Hypoproteinemia and hypoalbuminemia (<30g/L).

Additional complications

- Ovarian torsion.

Causes sudden, extreme abdominal pain and nausea. Incidence of 1/5000 stimulation cycles but more frequent if OHSS and if pregnancy are present (Mashiach et al., 1990).

- Ovarian bleeding

Caused by ovarian rupture or intraovarian bleeding, caused by pressure or bimanual examination. Causes signs of acute hemorrhage (hypotension, nausea, sudden drop in hematocrit).

- Thrombo-embolic symptoms

Both venous (65.7%) and arterial localisations have been described; 83% of these occur in neck-, arm- of head veins (60%); thrombosis also occurs in arteries veins of the lower body (Delvigne et al., 2003a); in 4-12% pulmonary embolism occurs (Stewart et al., 1997). Embolism has been described in the V. humeralis, subclavia, jugularis interna and cava; arterial ones in the A. subclavia, ulnaris, carotis interna and cerebri media and in the coronary arteries.

2.3 Primary risk factors

- 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 4-10mm in each ovary).
 - LH/FSH ratio >2 .
 - Hyperandrogenism
- History of OHSS
- Young patients
- Lean women
- Allergic predisposition

2.4 Secondary risk factors

- Maximum serum estradiol $>3000-4000$ pg/ml.
 - No clear cut-off value
 - Relatively poor predictive power (max. 73%).
 - Oestradiol itself is no mediator since OHSS is also possible with low serum oestradiol values (stimulation with recFSH)
 - The slope of the oestradiol rise is the main risk factor and is of more importance than the maximum level (PPV 77%).
- Number of follicles per ovary $>20-25$.
 - No clear cut-off value (10-35).
 - Variation dependent upon operator and technique.
- Measurements of the absolute VEGF (vascular endothelial growth factor)-serum concentration are not useful for individual prediction (Mathur et al., 2002).

2.3 Physiopathology

The physiopathology of the OHSS is increasingly better understood. The crux is an equilibrium between pro-angiogenic and anti-angiogenic factors present in follicular fluid. The pro-angiogenic role of the vascular endothelial growth factor (VEGF) is an important mediator of the syndrome (Pellicer et al., 1999; Garcia-Velasco and Pellicer, 2003). 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 concentrations in OHSS patients were shown to be increased (McClure et al., 1994; Abramov et al., 1997; Agrawal et al., 1999). 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 the OHSS (Neulen et al. 1995, 1998). Later it was shown that two VEGF-receptors exist (VEGFR-1 en 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 (Pellicer et al., 1999). Absolute serum concentrations have no value in the individual risk assessment because there

are individual variations in the binding of VEGF to its receptors (Mathur et al., 2002; Garcia-Velasco JA and Pellicer, 2003).

In rats, proof of concept was shown of a VEGF-2 inhibitor (SU5416) to block HCG-dependent VEGF-production (and ensuing neo-angiogenesis) (Gomez et al., 2002). 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 (Gomez et al., 2004).

The physiopathological cascade of the OHSS consists of: neo-angiogenesis and increased capillary permeability of the enlarged ovarian and other endothelial surfaces, fluid shift from the intravascular space to the extravascular space (abdomen, pleura, pericard), hemoconcentration, decreased renal clearance, oliguria/anuria, hyperviscosity of blood, modification in coagulation factors and thrombo-embolic risks. Hemoconcentration leads to an increase of the hematocrit, of the concentration of platelets and leucocytes, creatinin, ureum and liver enzymes in the plasma, as well as 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 starts to be secreted.

2.1 Classification

The *quantitative* aspects of the definition of the syndrome can not exactly be measured: ovarian dimensions can be assessed to a certain extent using echography, 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 used is the one proposed by Golan (Golan et al, 1989).

Classification of OHSS according to Golan (1989)			
OHSS			
Grade	Mild	Moderate	Severe
1.	Abdominal distention and discomfort		
2.	Criteria of grade 1 + nausea, vomiting, and/or diarrhoea. Ovaries enlarged 5-12 cm		
3.		Criteria of mild OHSS + echographic signs of ascites	
4.			Criteria of moderate OHSS + clinical signs of ascites and/or hydrothorax and respiratory distress
5.			All of the above + changes in blood volume and viscosity, hemoconcentration, coagulation disorders and decreased renal output and function
6.			Life-threatening form

Subsequently, two further refinements were introduced: “**critical OHSS**” (Navot et al., 1992) and “**group C severe OHSS**” (Rizk and Aboulghar, 1999), who both describe the same *life threatening* clinical entity: severe reduction in circulating volume, severe hemoconcentration, multiple organ failure (kidney, liver, heart) and/or thrombo-embolic 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%**.

2. PREVENTION

3.1 Primary prevention.

Patients who have a primary risk for OHSS should be exposed to gonadotropins as little as possible. This implies that all other more safe treatments should have had fair chances: life style changes (diet and exercise), oral ovulation induction, use of pulsed GnRH, laparoscopic ovarian surgery. 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.

Identification of women with thrombophilia, a family history of thrombo-embolism and women with antiphospholipid antibodies should ideally be performed 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 oestradiol measurements. All patients at risk should be informed orally and in written so that at the occurrence of early symptoms, they should consult the responsible gynaecologist and not an inexperienced physician.

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

3.2 Secondary prevention.

3.2.1 Cycle cancellation.

In ovulation-induction withholding HCG prevents the early form of OHSS. Avoiding HCG and intercourse/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 without reimbursement. In very severe cases with poor follow-up possibilities, however, it may be the only method to avoid disaster.

3.2.2 Coasting (“Soft landing”)

Principle

When high risk patients rapidly reach high (>3000 pg/ml) serum oestradiol levels with a large number (>20 per ovary) of follicles during stimulation, gonadotropin administration can be decreased or stopped while continuing Gn-RH agonist administration. This allows larger follicles to continue to grow, whereas 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 (Fluker et al., 1999). 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, without influence on oocyte quality and endometrial receptivity (Garcia-Velasco et al., 2004).

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 (Delvigne et al, 2001). 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.

Criteria for coasting

Criteria for coasting are based on a relationship between the number of growing follicles and/or the serum oestradiol levels and the risk for OHSS. There are two criteria for decision: the serum-E₂-levels determines whether coasting is done or not; the echographic image determines when.

Serum oestradiol levels

Most authors use values between 2500-3000 pg/ml. *Continuing gonadotropins at a serum oestradiol level of >3000 pg/ml is considered not good clinical practice.* When using recFSH, oestradiol values tend to be lower and the above criteria do not hold. It has therefore been suggested that the oestradiol value should come into play only if at the same time 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 15mm, coasting will result in an abrupt stop in follicle development and a quick serum E₂-decrease. On the other hand, when the majority of follicles are >15mm at the start of coasting, a number of cystically enlarged follicles with decreased oocyte quality may ensue (Sher et al., 1995). Hence the *rule of the golden middle way*: coasting should start when ~50% of the follicles are ~15mm in diameter and have become independent of further gonadotropin stimulation.

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 (Ulug et al., 2002), but this remains controversial (Sher et al., 1995; Delvigne et al., 2003b). Further clinical research is desirable to assess the subtleties with respect to oocyte numbers and quality and endometrial receptivity.

3.3.3 Modification of the ovulation triggering agent.

Although good data are lacking, it is not impossible that lower doses of HCG than those usually utilized (5000 or 10.000 IU) 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 the (early form of) OHSS. An endogenous LH surge can be provoked by the administration of a short-acting GnRH agonist (Empeaire en

Edwards, 2004). This only possible in cycles without pituitary desensitization by a GnRH agonist. The 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 commercialise this (available) product for this indication. So it 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.

3.3.4 Administration of macromolecules.

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%) versus 89 OHSS cases in 611 untreated risk cycles (14.6%) (Delvigne et al., 2003). The Cochrane review also shows that IV albumin administration at the time of oocyte collection has a preventive effect in cycles with a severe risk for OHSS (Aboulghar et al., 2002). However, a recent prospective randomized trial of 488 cases in each arm of the study seems to prove the inefficiency of human albumin (Bellver et al., 2003). Two studies show a decreased pregnancy rate after the use of IV albumin (Shaker et al., 1996; Costabile et al., 2000). Albumin administration also has side effects: viral transmission, nausea, vomiting, febrile and allergic reactions, and it is expensive.

Hydroxyethyl starch solution (HEAS)

Because of the risk of viral transmission with human albumin, some authors have tested the effect of a safer non-biological substitute with comparable physiological properties: HEAS. Three studies suggest a useful effect but the cohorts are too small to draw definite conclusions (Graf et al., 1997; Knig et al., 1998; Gökmen et al., 2001). Further clinical research seems warranted.

3.3.5 Cryopreservation of all embryos.

Instead of cancelling 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 does decrease the risk as well. The Cochrane review concludes that the present evidence is insufficient to consider this approach as the standard of treatment (D'Angelo en Amso, 2002). It may be considered when coasting has not been applied when it should have 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 has a high risk for the late form of OHSS.

3.3.5 Summary

No method can prevent all cases of OHSS, apart from withholding HCG, still

the ubiquitous ovulation triggering agent, although other molecules exist (rLH) but are either not available or very expensive. In practice, in ART 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 avoid completely OHSS (Isik et al., 2001). Single embryo transfer after ART prevents multiple pregnancies but not the OHSS (De Neubourg et al. 2004).

3. CLINICAL MANAGEMENT.

4.1 Criteria for hospitalisation

- Hematocrit >45%
- Any sign of severe OHSS

4.2 Elements of outpatient follow-up

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

4.3 Elements of hospital follow-up

- Heartrate
- Blood pressure
- Daily fluid balance
- Echografic assessment: ascites volume, ovarian dimensions
- RX thorax (if dyspnoeic) to diagnose pleural effusion
- ECG (to exclude pericardiac effusion)
- Hematological examination: hematocrit, RBC count, WBC count, electrolytes, kidney function tests, liver enzymes, total serum protein and albumin, coagulation tests

4.4 Treatment strategy

4.4.1 Maintain diuresis!

Fluid management

- Intravenous administration of Ringer lactate solution
- First 24 hours: 1500-3000ml. In order to avoid overadministration of fluid, some centres restrict total fluid intake (inclusive oral) to 1500ml.
- Subsequent days: fluid volume in function of fluid balance

- Combination of Ringer lactate + Dextrose 5% solution or NaCl 0.9% + Dextrose 5% (standard) solution

Plasma expanders

- HEAS (hydroxyethyl starch) 6% solution in isotonic NaCl.
- Maximal daily dose: 33ml/kg in 250-500 ml per day, dropwise, utilising slow administration to avoid lung congestion.

Albumin administration

- Is only started if hypo-albuminemia (<28mg/dl) is demonstrated because of the risk for hepatitis, overdosage with albumin, renal function disorders and high cost. Should definitely be started when ascitic fluid is punctured because this causes huge loss of protein.

4.4.2 Anticoagulant drugs

Low-molecular weight heparin preparations are preferably given primarily in all cases of severe OHSS with hospitalisation but certainly if:

- Clinical signs of thrombo-embolic complications
- Documented thrombophilia
- History of hypercoagulability or thrombo-embolism
- Uncorrected hemoconcentration after 48 hours of usual intravenous treatment

As a prevention of thrombo-embolic complications, especially in patients who are immobilized due to obesity or other reasons, low-dose aspirin administration has been suggested. When ascites puncture is performed, this has to be weighed against the risk for bleeding.

4.4.4 Ascites drainage

Can be performed both abdominally and vaginally (Padilla et al., 1990; Aboulghar et al., 1990), but always under sonographic guidance. It is considered when there is severe abdominal discomfort and dyspnoea and results in quick subjective relief for the patient. It also results in an increased venous return, increased cardiac output, diuresis, creatinin clearance and lung ventilation. It should be performed gradually: maximum 4 litres over 12 hours. Removal of large quantities means losing huge amounts of protein which must be substituted. One litre of ascites fluid contains 3.0-3.5 g of albumin; daily 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 an expert centre. Hospitalized patients must be visited frequently by the same physician as the clinical picture may change quickly (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 beginning pregnancy should be considered.

4.5 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 cycles, with many oocytes and good quality embryos. Several authors have reported an increase in early pregnancy loss in OHSS patients (Raziel et al., 2002; Papanikolaou et al., 2004).

4. CONCLUSIONS AND RECOMMENDATIONS

Although theoretically known, OHSS remains underestimated because the perceived incidence per gynaecologist 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 sequelae are rare, they are serious (thrombo-embolism). Although fatal cases are rare, they go unreported and so may be underestimated and they are never in proportion to the indication for treatment (infertility in young healthy women).

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 treatment): low dose step-up regimen, step-down regimen, or use antagonists, always utilising blood and sonographic control of ovarian response.
3. HCG as an ovulation trigger should be replaced by safer methods (rLH, endogenous GnRH-surge by an agonist); they exist but are not commercially available.
4. In IVF/ICSI the principle of obtaining “as many oocytes as possible” should be replaced by softer stimulation regimens aiming at less oocytes of good quality.
5. In risk situations the patient should be informed about possibilities such as cancelling, coasting or freezing for subsequent replacement.
6. When signs of OHSS occur, the patient must be completely informed and hospitalization should be proposed at the slightest deterioration.
7. These patients belong in a hospital ward where the clinical picture is known 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 programmes as well as after ovulation induction.

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