Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials


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STUDY QUESTION: What is an objective approach that employs measurable and reproducible physiologic changes as the basis for the classification of ovarian hyperstimulation syndrome (OHSS) in order to facilitate more accurate reporting of incidence rates within and across clinical trials?

SUMMARY ANSWER: The OHSS flow diagram is an objective approach that will facilitate consistent capture, classification and reporting of OHSS within and across clinical trials.

WHAT IS KNOWN ALREADY: OHSS is a potentially life-threatening iatrogenic complication of the early luteal phase and/or early pregnancy after ovulation induction (OI) or ovarian stimulation (OS). The clinical picture of OHSS (the constellation of symptoms associated with each stage of the disease) is highly variable, hampering its appropriate classification in clinical trials. Although some degree of ovarian hyperstimulation is normal after stimulation, the point at which symptoms transition from those anticipated to those of a disease state is nebulous.

STUDY DESIGN, SIZE, DURATION: An OHSS working group, comprised of subject matter experts and clinical researchers who have significantly contributed to the field of fertility, was convened in April and November 2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The OHSS working group was tasked with reaching a consensus on the definition and the classification of OHSS for reporting in clinical trials. The group engaged in targeted discussion regarding the scientific background of OHSS, the criteria proposed for the definition and the rationale for universal adoption. An agreement was reached after discussion with all members.

MAIN RESULTS AND THE ROLE OF CHANCE: One of the following conditions must be met prior to making the diagnosis of OHSS in the context of a clinical trial: (i) the subject has undergone OS (either controlled OS or OI) AND has received a trigger shot for final oocyte maturation (e.g. hCG, GnRH agonist [GnRHa] or kisspeptin) followed by either fresh transfer or segmentation (cryopreservation of embryos) or (ii) the subject has undergone OS or OI AND has a positive pregnancy test. All study patients who develop symptoms of OHSS should undergo a thorough examination. An OHSS flow diagram was designed to be implemented for all subjects with pelvic or abdominal complaints, such as lower abdominal discomfort or distention, nausea, vomiting and diarrhea, and/or for subjects suspected of having OHSS. The diagnosis of OHSS should be based on the flow diagram.

LIMITATIONS, REASONS FOR CAUTION: This classification system is primarily intended to address the needs of the clinical investigator undertaking clinical trials in the field of OS and may not be applicable for the use in clinical practice or with OHSS occurring under natural circumstances.

WIDER IMPLICATIONS OF THE FINDINGS: The proposed OHSS classification system will enable an accurate estimate of the incidence and severity of OHSS within and across clinical trials performed in women with infertility.
**Introduction**

Ovarian hyperstimulation syndrome (OHSS) is a potentially lethal iatrogenic complication of the early luteal phase or/and early pregnancy after ovulation induction (OI) or ovarian stimulation (OS). The incidence of clinically significant OHSS is 2–3%, and milder forms may develop in up to 20–30% of all in vitro fertilization (IVF) patients (Papanikolaou et al., 2006). In comparison with long gonadotrophin-releasing hormone (GnRH) agonist (GnRHa) protocols, the risk of severe OHSS is reduced by ~50%, using GnRH antagonists for co-treatment during OS prior to IVF or intra-cytoplasmic sperm injection (ICSI) treatment; importantly, both protocols provide equal efficacy in terms of reproductive outcome. Nevertheless, moderate or severe OHSS may still occur in GnRH antagonist protocols, primarily if human chorionic gonadotrophin (hCG) is administered to trigger final oocyte maturation in high-responder patients (Tarlatzis et al., 2012).

A recent consensus conference was convened in Harbin, China with the goal of modifying the CONSORT checklist to improve the quality of reporting of clinical trials that test infertility treatments (Harbin Consensus Conference Workshop Group). The group identified OHSS resulting from OI or OS as a potential harm that merits reporting in clinical trials (Harbin). This is challenging since the clinical picture of OHSS (i.e. the constellation of symptoms associated with each stage of the disease) is highly variable, hampering the appropriate capture and uniform classification of OHSS in the clinical research setting. Whereas some degree of ovarian hyperstimulation is expected with the use of follicular stimulants, the point at which symptoms transition from anticipated effects to those indicative of a disease state is nebulous.

The aim of this report is to describe an objective approach that employs measurable and reproducible physiologic changes as the basis for the classification of OHSS, in order to facilitate more accurate reporting of incidence rates within and across clinical trials performed in women with infertility.

**OHSS**

**Pathophysiology**

The primary physiologic change underlying OHSS is an increase in vascular permeability, resulting in fluid shift from the intravascular to third space compartments (Tollan et al., 1990; Goldsman et al., 1995; Geva and Jaffee, 2000). Pro-angiogenic vascular endothelial growth factor (VEGF) is an important mediator of OHSS (Pellicer et al., 1999; Garcia-Velasco and Pellicer, 2003), and serum VEGF levels have been shown to correlate with OHSS severity (Geva and Jaffee, 2000). In addition, hCG has been shown to increase VEGF expression in human granulosa cells, with related increases in VEGF concentration (Neulen et al., 1995; Pellicer et al., 1999). Other mediators that have been implicated in the pathogenesis of OHSS include angiotensin II, insulin-like growth factor I and interleukin-6 (The Practice Committee of ASRM, 2006).

**Risk factors**

The factors associated with an increased risk of OHSS include young age (<30 years) (Navot et al., 1988), low-body weight, polycystic ovary syndrome (PCOS) or high basal antral follicle count (AFC) (Brinsden et al., 1995; Enskog et al., 1999; Humaidan et al., 2010), elevated or rapidly increasing serum estradiol levels during OS (Delngvne and Rozenberg, 2002), history of an elevated response to gonadotrophins (prior hyper-response or OHSS) (Navot et al., 1992), a large number of small follicles (8–12 mm) during OS (Navot et al., 1988), the use of hCG instead of progesterone for luteal phase support after IVF (Navot et al., 1992), a large number of oocytes retrieved (>20) (Asch et al., 1991), early pregnancy (Enskog et al., 1999) and high basal anti-Müllerian hormone (AMH) concentrations (Humaidan et al., 2010). Finally, ethnicity also seems to play a role, as African-American women undergoing IVF have been reported to be at greater risk of developing OHSS than Hispanic or Caucasian women (Luke et al., 2009).

**Clinical presentation**

The two types of OHSS are early onset, appearing <10 days after hCG administration, which is self-limited when no pregnancy occurs, and late onset, appearing ≥10 days after oocyte retrieval (Mathur et al., 2000). Early onset OHSS is associated with ovarian hyper-response to gonadotrophin stimulation in patients predominantly triggered with hCG, whereas late onset OHSS is induced by hCG produced by the trophoblast of an implanting embryo. Cases comprised of early onset followed by late onset OHSS are often serious and prolonged (Papanikolaou et al., 2006).

The clinical diagnosis of OHSS has been classified into different grades based on severity (Golan, 2009); however, it is of note that these grades...
are not strictly separated and can quickly transition. Most cases of OHSS are mild, self-limited and not of clinical concern. Symptoms of OHSS may begin as early as 24 h after the administration of hCG and increase in severity over the next 7–10 days, usually related to the rise in endogenous hCG from early pregnancy (Delvigne and Rozenberg, 2003).

The initial presentation of OHSS typically includes abdominal distension due to increased ovarian size; a progressive increase in abdominal circumference occurs as a result of accumulation of intra-peritoneal fluid. Increased OHSS severity is the result of a further increase in vascular permeability and ascites leading to hemococoncentration. The associated reduction in intravascular volume may result in oliguria (Fabregues et al., 1998).

As OHSS increases in severity, abdominal distension due to ascites may become more apparent, and enlarged ovaries filled with multiple corpus luteal cysts may be detected via ultrasound. Electrolyte imbalance is often observed in severe OHSS (Rahami et al., 1997). In critical cases, women with pleural effusion may present with tachypnea or shortness of breath and untreated large pleural effusions have resulted in adult respiratory distress syndrome (Abramov et al., 1999). Thromboembolism is the most severe complication associated with OHSS (Hignett et al., 1995), and fatal cases have been reported (Cluroe and Synek, 1995). Thus, although OHSS reporting is a gray zone, a mortality rate of 3/100 000 after IVF/ICSI has been estimated in Europe (Braat et al., 2010).

Prevention

Although it is not possible to completely eliminate OHSS, significant reductions in incidence can be achieved with early identification of risk factors and careful clinical management of women undergoing OS. Prevention measures for OHSS are categorized into primary and secondary types. Primary prevention strategies focus on personalizing the stimulation protocol to an individual patient’s risk factors for ovarian response. Secondary prevention strategies are used to avoid OHSS in patients who have had an excessive response to OS.

For the primary prevention of OHSS, exposure to gonadotrophins should be tailored according to AMH and AFC in first treatment cycles (Humaidan et al., 2010) or previous responses to OS with exogenous gonadotrophins. Women with PCOS, a history of OHSS, thrombophilia, family history of thromboembolism and antiphospholipid antibodies should be identified prior to the initiation of OS, and treatment in these women should proceed at the lowest effective gonadotrophin dose with routine monitoring (frequent vaginal ultrasonography and/or serum estradiol measurements). A variety of protocols have been used to accomplish this goal, including low-dose step-up, limited OS, mild stimulation treatment and withholding FSH on the day of hCG trigger. An important primary OHSS prevention strategy is the use of GnRH antagonist protocols. Current scientific evidence supports the hypothesis that GnRH antagonist co-treated cycles result in a significantly lower incidence of OHSS relative to GnRHa cycles. It is important that each woman undergoing treatment with gonadotrophins be informed of her personal risk for OHSS, and encouraged to obtain a medical consultation at the occurrence of symptoms.

The latest and probably most efficient secondary OHSS prevention strategy is GnRHa triggering of final oocyte maturation. The use of GnRHa for the trigger secures sufficient oocyte maturation and significantly reduces, and in most cases, eliminates the risk of OHSS. However, the GnRHa trigger can only be applied to cycles co-treated with a GnRH antagonist, which are the minority of cycles since the long GnRHa down-regulation protocol is still the most preferred protocol by clinicians worldwide (Tobler et al., 2014). Recently, kisspeptin was used to trigger final oocyte maturation in patients at risk of OHSS development; however, more data are needed to draw firm conclusions as to this novel trigger concept (Abbara et al., 2015). Another modification includes lowering the dose of hCG used for trigger, although this does not reduce the risk of late onset OHSS (Humaidan et al., 2010).

Additional secondary prevention strategies include cycle cancellation (withholding hCG), segmentation (cryopreservation of embryos) and administration of macromolecules. In cycle cancellation, withholding hCG for OI prevents the early and late forms of OHSS. In GnRHa co-treated cycles, cancellation is a difficult decision; however, it may be the preferred method to avoid deleterious consequences in patients with an extreme ovarian response to stimulation. In segmentation, a bolus of GnRHa is administered, oocytes are retrieved and all embryos are frozen (Devroey et al., 2011; Maheshwari and Bhattacharya, 2013). Although this approach does not completely eliminate the risk of early OHSS (Fatemi et al., 2014; Gurbuz et al., 2014; Ling et al., 2014), it does avoid the late form of OHSS associated with pregnancy. Finally, prophylactic administration of macromolecules, such as hydroxethyl starch solution (HEAS), has been suggested to reduce the risk of OHSS development by increasing the plasma osmotic pressure and binding mediators of ovarian origin (Graf et al., 1997; Knig et al., 1998; Gokmen et al., 2001; Aboulghar et al., 2002; Bellver et al., 2003; Delvigne et al., 2003). However, recent studies show an increased risk of mortality in patients with sepsis (Westphal et al., 2009; Public Workshop, 2015) and an increased risk of kidney injury requiring dialysis in critically ill patients (Westphal et al., 2009; Van Der Linden et al., 2013; Public Workshop, 2015) following treatment with HEAS, warranting a careful risk–benefit assessment prior to its use (Westphal et al., 2009; Van Der Linden et al., 2013; Public Workshop, 2015). The available macromolecule studies are limited by small sample sizes and disparate results, underlining the need for additional clinical research.

Treatment

The treatment approach for the clinical management of OHSS is multifaceted and individualized based on disease severity and progression. Once the diagnosis of OHSS has been made, the disease severity should be determined. Outpatient management is recommended for women with milder forms of OHSS. The elements of outpatient follow-up include daily fluid balance, daily weighing, assessment of increase in umbilical abdominal circumference, blood tests and ultrasound examination every 48–72 h and instruction to contact the clinic at any sign of deterioration. Outpatient culdocentesis/paracentesis should be considered to prevent OHSS disease progression on a case-by-case basis.

The criteria for hospitalization due to OHSS are hematocrit > 45% and/or any sign of pulmonary or hemodynamic compromise. Inpatient treatment of OHSS includes maintenance of diuresis with fluid management and administration of albumin if indicated due to hypo-albuminemia (< 28 mg/dl); administration of anti-coagulant drugs in patients with a documented history of thrombophilia, hypercoagulability or thromboembolism, or uncorrected hemoconcentration after 48 h of usual intravenous treatment; and culdocentesis/paracentesis. Hospitalized patients must be visited frequently, as the clinical picture may change rapidly. When critical OHSS develops, the patient must be admitted to...
the intensive care ward. Only in very critical cases should interruption of an early pregnancy be considered. Treatment with cabergoline (0.5 mg daily for 8 days) (Alvarez et al., 2007; Gaafar et al., 2014) and cabergoline with a GnRH antagonist (0.5 mg orally for 7 days plus 250 mcg ganirelix SC daily for 2 days) (Rollene et al., 2009) have been recommended to reduce the VEGF and, subsequently, the effects of OHSS.

Review of existing published classification

A detailed classification for OHSS was first proposed by Rabau et al. (1967), which was later reorganized by Schenker and Weinstein (1978), based on clinical presentation and laboratory findings. This early classification system divided the syndrome into three categories (mild, moderate and severe) and six grades of severity. In 1989, a revised OHSS classification system was proposed by Golan et al., which included four major modifications to the earlier system: (i) urinary assays of hormones were omitted; (ii) the diagnosis of ovarian enlargement and the detection of ascites were ultrasound based; (iii) nausea, vomiting and diarrhea and abdominal distension were moved from moderate to mild (Grade 2) OHSS and (iv) the detection of ascites by transvaginal ultrasonography established the diagnosis of moderate OHSS (Grade 3).

Additional refinements have since been published. In 1992, Navot et al. defined a ‘critical’ category of OHSS and, in 1999, Rizk and Aboulghar subcategorized severe OHSS into three Grades (A, B and C), with ‘Grade C’ being the most severe form. Both updates describe life-threatening OHSS, including complications such as renal failure, thromboembolism and adult respiratory distress syndrome. These symptoms are considered as ‘Grade 6 OHSS’ in the modern classification by Golan (2009). In 2010, Humaidan et al. provided a classification scheme for grading OHSS that incorporates vaginal sonography and laboratory parameters to objectively relate symptoms to severity (Humaidan et al., 2010). In this system, mild, moderate and severe forms of OHSS are distinguished by the extent of fluid shift into body cavities, with moderate disease defined by shifts of <500 ml, and severe disease characterized by laboratory signs of hepatorenal dysfunction due to hemoconcentration and hypovolemia (Humaidan et al., 2010). The authors offered practical, evidence-based guidance to reduce the occurrence of OHSS, and cited GnRH antagonist protocols and GnRHa trigger as the most important risk reduction strategies, and very effective when used in combination (Humaidan et al., 2010). Recently, the Royal College of Obstetricians & Gynaecologists published updated evidence-based guidelines to help clinicians diagnose and manage patients with OHSS (Green-top Guideline, 2016).

Methods

An OHSS working group, comprised of subject matter experts and clinical researchers who have significantly contributed to the field of fertility, was convened in April and November 2014. The scientific advisory group was tasked with reaching a consensus on the definition and classification of OHSS.

![Figure 1](http://humrep.oxfordjournals.org/)

**Figure 1** Ovarian hyperstimulation syndrome (OHSS) flow diagram for use in the clinical trial setting. †Exaggerated response, as defined by World Health Organization criteria. ‡Subjects to be screened for OHSS symptoms on the day of embryo transfer, the day of positive pregnancy test or at the time of complaint. Shaded shapes denote required reporting of group in the context of a clinical trial. LFT, liver function test; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Cr, creatinine.
OHSS for reporting in clinical trials. The group engaged in targeted discussion regarding the scientific background of OHSS, the criteria proposed for the definition and the rationale for universal adoption. An agreement was reached after discussion with all members.

**Classification of OHSS in the clinical trial setting**

Current classification systems are inadequate to uniformly capture OHSS in the clinical research environment, as they are often subjective and do not account for the wide variations in the presentation of OHSS. Thus, the following OHSS flow diagram is proposed to facilitate consistent capture, classification and reporting of OHSS in the clinical trial setting (Fig. 1).

In a clinical trial, one of the following conditions must be met prior to making the diagnosis of OHSS: (i) the subject has undergone OS (either controlled OS or OI) AND has received an hCG, GnRHa or kisspeptin trigger; or (ii) the subject has undergone OS or OI AND has a positive pregnancy test (Table I).

Following OS, the response may be either exaggerated or normal (Zegers-Hochschild et al., 2009; Personal communication S. Vanderpoel [WHO] to B. Stegmann, 2015). Women with exaggerated responses to stimulation are at increased risk of OHSS, and although this risk may be mitigated with the use of a GnRHa trigger, this group still represents a potential excessive response to treatment, which warrants reporting in the clinical trial setting. Women with a normal response to stimulation receive an hCG trigger, and are screened for symptoms and signs of OHSS on the day of embryo transfer, the day of a positive pregnancy test and/or at the time of complaint.

Screening may reveal classic symptoms of OHSS (nausea, vomiting, abdominal discomfort and/or bloating) and/or clinical signs of OHSS (weight gain, tachycardia/orthostatic changes, tachypnea with dyspnea). The presence of these symptoms and/or signs alone is not sufficient to make a diagnosis of OHSS, and additional screening tests (ultrasound for ascites, liver function tests, electrolytes, hematocrit, serum creatinine (Cr), 24-h urine output) are necessary.

A woman without any positive findings on additional screening is considered an ovarian hyper-responder, not a diagnosed case of OHSS. For these women, continued surveillance is warranted, and reporting in the clinical trial is encouraged. In contrast, even one positive finding at additional screening along with classic symptoms and/or clinical signs of OHSS is sufficient to make the diagnosis of OHSS. Women in this group require close monitoring, and reporting in the clinical trial is required.

Once it is determined that OHSS is present, it is further classified into self-limited OHSS or OHSS with significant co-morbidities. In self-limited OHSS, the disease eventually resolves completely, without the development of significant or permanent comorbidities. Some treatments such as culdocentesis or prophylactic anticoagulation may be required, but the disease does not progress to a catastrophic event. When a

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**Table I: References for quantitative abnormalities in Fig. 1.**

<table>
<thead>
<tr>
<th>Examination findings</th>
<th>Significant alterations</th>
<th>Normal range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>≥ 2 lbs (0.91 kg)/day for 2 days or a total increase of 5 lbs (2.27 kg) from the beginning of the stimulation period</td>
<td>—</td>
<td>Practice Bulletin ASRM</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Over 100 beats/min</td>
<td>Varies by patient</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Over 20 breaths/min at rest</td>
<td>12–20 at rest</td>
<td>Mosby’s Medical Dictionary, 8th edition</td>
</tr>
<tr>
<td>Oliguria</td>
<td>&lt;0.5 ml/kg/h for &gt;6 h or a 24-h negative fluid balance of 500 ml</td>
<td>varies</td>
<td>Acute Kidney Injury Network (AKIN) Guidelines</td>
</tr>
<tr>
<td>Ascites</td>
<td>Grade 1: Visible only on US or CT*</td>
<td>No fluid present</td>
<td>Moore et al. (2003)</td>
</tr>
<tr>
<td></td>
<td>Grade 2: detectable with flank bulging or shifting dullness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3: marked distension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Sodium: &lt;132 mEq/l</td>
<td>135–145 mEq/l</td>
<td>Practice Bulletin ASRM</td>
</tr>
<tr>
<td></td>
<td>Potassium: &gt;5.0 mEq/l</td>
<td>3.5–5.0 mEq/l</td>
<td>Practice Bulletin ASRM</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hematocrit: over 45% or evidence of a &gt;10% increase in HCT</td>
<td>36–46%</td>
<td>Practice Bulletin ASRM</td>
</tr>
<tr>
<td>Renal function</td>
<td>Serum Creatinine (SCr): Increase in SCr ≥ 0.3 mg/dl or increase to ≥150% above initial baseline levels</td>
<td>0.6–1.1 mg/dl</td>
<td>Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines</td>
</tr>
</tbody>
</table>

*Either abdominal or transvaginal scan.
Conclusions and future recommendations

The universal adoption of consistently applied criteria by which to define OHSS utilizing the OHSS flow diagram for future clinical trials has the goal of producing homogeneous results, reducing bias caused by spurious definitions and enabling valid comparisons within and across clinical trials on which to base reliable conclusions. The uniformity of the resulting data would be expected to increase transparency of the risk–benefit ratio of infertility treatments and ultimately improve medical care. This standard approach should also enable an accurate means by which to estimate the true incidence and severity of OHSS. Future studies should be designed to implement the OHSS flow diagram and measure outcome. Importantly, this process of diagnosing OHSS is primarily intended to address the needs of the clinical investigator undertaking clinical trials in the field of OS.

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Authors’ roles

All authors substantially contributed to analyzing and interpreting the data, drafting the manuscript and/or critically revising it for important intellectual content, and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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Conflict of interest

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