Preventing ovarian hyperstimulation syndrome: guidance for the clinician

Fertility and Sterility 2010; 94:389–400

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OHSS
(all ovarian stimulation protocol result in some degree of hyperstimulation)

- iatrogenic complication of ovulation induction (OI) and ovarian stimulation for ART
  - Cystic enlargement of ovaries and rapid fluid shift from intravascular compartment to 3rd space
  - Life-threatening in severe form → hospitalization rate of 1.9%
  - hCG (exogenous or endogenous) as triggering factor, mediated via VEGF
The pathogenesis of OHSS.
• Current guidelines for prevention do not encompass the most recent advances in the literature.
• To review the most recent evidence supporting different OHSS reduction strategies:
  – **Pubmed**, published in the last 5 years
## Classification

*(clinically)*

<table>
<thead>
<tr>
<th></th>
<th>Early OHSS</th>
<th>Late OHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>onset</strong></td>
<td>$\leq 9$ days after oocyte retrieval</td>
<td>$&gt; 10$ days</td>
</tr>
</tbody>
</table>
| **reason**    | Correlate to ovarian response to *exogenous hCG* stimulation | 1. Correlate to *endogenous hCG* produced by implanting embryo  
|               |                                                 | 2. Administration of hCG for *luteal phase support* (LPS) |
# OHSS severity classification
(by TVS + lab)

<table>
<thead>
<tr>
<th>Proposed new clinical grading system for OHSS.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
</tr>
<tr>
<td><strong>Objective criteria</strong></td>
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<tr>
<td>Fluid in Douglas pouch</td>
</tr>
<tr>
<td>Fluid around uterus (major pelvis)</td>
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<tr>
<td>Fluid around intestinal loops</td>
</tr>
<tr>
<td>Hematocrit &gt; 45%</td>
</tr>
<tr>
<td>White blood cells &gt; 15,000/mm³</td>
</tr>
<tr>
<td>Low urine output</td>
</tr>
<tr>
<td>&lt;600 mL/24 h</td>
</tr>
<tr>
<td>Creatinine &gt; 1.5 mg/dL</td>
</tr>
<tr>
<td>Elevated transaminases</td>
</tr>
<tr>
<td>Clotting disorder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Subjective criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Pelvic discomfort</td>
</tr>
<tr>
<td>Breathing disorder</td>
</tr>
<tr>
<td>Acute pain</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Ovarian enlargement</td>
</tr>
<tr>
<td>Pregnancy occurrence</td>
</tr>
</tbody>
</table>

*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.

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**Life threatening severe OHSS:**
- hepatorenal failure
- acute respiratory distress
- hemorrhage from ov rupture
- thromboembolism

**Rapid weight gain (> 1kg/day)**
presentation and management

• mild OHSS is relatively common in stimulated cycles

• Ovarian enlargement on TVS is a key indicator of severity after OI.
  – less indicative in IVF as follicle aspiration (→ ov ↓)

• Most can be managed on an outpatient basis:
  – oral analgesics and antiemetics
  – patient education
  – careful monitoring daily: PE, sono, BW, Hct, e-, Cr
• In nonconception cycles: mild or moderate OHSS likely to resolve spontaneously after menstruation

• **Pregnant**: ↑ endogenous hCG → ↑ risk of severe OHSS
  – Hospitalization
  – IV fluid
  – Ascites puncture
  – Prophylactic measures to prevent thromboembolism
Predicting OHSS: identifying the at-risk patient

• Change of ovarian stimulation regimen / other preventative measures

• Primary risk factor (patient related)

• Secondary risk factor (ovarian response related)
Primary risk factors (1)

- **AMH**
  - expressed in granulosa cells from preantral and small antral follicles → ovarian reserve
  - more accurate predictor of normal ovarian response than age, FSH, or inhibin-B alone or in combination
  - All cycle cancellations due to OHSS risk were in pts with highest AMH quartile → as OHSS predictor

  *Hum Reprod 2007;22:766–71*

  - better predictor of OHSS than age and BMI
  - Cut-off value: 3.36 ng/mL (sensitivity: 90.5%; specificity: 81.3%) → international standard needed
### Primary risk factors (2)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>High basal AMH</td>
<td>Cut-off level of 3.36 ng/mL has a sensitivity of 90.5% and specificity of 80% in predicting OHSS (8)</td>
</tr>
<tr>
<td>Regression analysis has proven that receiver operating characteristic curve is superior to age, number of follicles (8)</td>
<td></td>
</tr>
<tr>
<td>High AFC</td>
<td>AFC &gt; 14 may predict hyperresponse (48)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;33 y (8)</td>
</tr>
<tr>
<td>Previous OHSS</td>
<td>Moderate or severe cases especially when hospitalization required</td>
</tr>
<tr>
<td>History</td>
<td>Yes</td>
</tr>
<tr>
<td>PCOS/isolated PCOS characteristics</td>
<td>≥ 12 antral follicles 2–8 mm in diameter is predictive (46)</td>
</tr>
<tr>
<td>“necklace” sign</td>
<td>high # of follicle recruited</td>
</tr>
</tbody>
</table>

• AFC (antral follicle count)
  - Alone and in combination for predicting ovarian response comparable
  - >14 may predict hyperresponse (sensitivity: 82%; specificity: 89%)
Secondary risk factors
ovarian response parameters

1. Absolute level or rate of increase of serum E2
2. Follicle size and #: >14 follicles of 11 mm; > 11 follicles of 10 mm
3. VEGF: conflicting result → no applicable
4. ↑ inhibin-B: potential candidate, may prime the follicle to overresponse to hCG (mechanism ?)

• None to be independently predictive of OHSS, combination ? ? 1+2 ??
Preventing OHSS: better than cure

• Complete prevention is still not possible!!
• Early identification of risk factors and careful monitoring \(\rightarrow \downarrow\) incidence

• **Primary prevention**: stimulation protocol personalized after assessment of primary risk factors to classify pts as poor, normal or high responders

• **Secondary prevention**: based on ovarian response to involve withdrawal, delay, or modification of protocol to avert OHSS
Primary prevention

1. Reducing exposure to gonadotropins
   a. Reducing dose (IUI cycles) – low-dose gonadotropin protocol in PCOS
      – **Aim**: to facilitate a single dominant follicle rather than multiple follicles
– low-dose step-up protocol:
  • starting FSH (75 IU) for 14 days, followed by small ↑ at interval ≥ 7 days until follicle development initiated, dose continued until ovulation triggering
  • higher rate of monofollicular development, fewer cycle cancelled owing to hyperstimulation, lower incidence of OHSS and multiple pregnancy
b. Reducing duration of FSH exposure (IVF/ICSI cycles)

- **FSH tx duration? no consensus →** wide variation in individual response

- **When to stop gonadotropin therapy and trigger final oocyte maturation?**

- **Whether FSH should be given on the day of hCG administration?**
– Prospective RCT in 413 IVF pts cotreated with GnRH antagonist
  • Delaying triggering and continuing FSH had a negative impact on pregnancy rates
  • Once primary follicle reach the criteria for triggering, additional FSH is not necessary and may be detrimental to outcome (possibly due to negative impact on endometrial receptivity)

_Hum Reprod 1999;14:1457–60_
- **mild stimulation protocol:**
  - administration of FSH delayed until mid to late follicular phase
  - early attempts at natural cycle or minimal stimulation protocols resulted in high cancellation rate owing to *premature luteinization* → + GnRH antagonist for late-cycle suppression of pituitary gonadotropin release → improved outcome
<table>
<thead>
<tr>
<th></th>
<th>Normo-responder (404 pts, 769 cycles)</th>
<th>Mild stimulation protocol with single ET (444)</th>
<th>Long agonist protocol with double ET (325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. offer benefits</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. further RCTs</td>
<td></td>
<td></td>
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<tr>
<td>intervention</td>
<td>FSH from D5 and GnRH antagonist cotreatment when at least one follicle $\geq$ 14 mm</td>
<td></td>
<td>As traditional protocol</td>
</tr>
<tr>
<td>OHSS</td>
<td>6 (1.4%)</td>
<td>12 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Cumulative live birth rate</td>
<td>43.4%</td>
<td>44.7%</td>
<td></td>
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<tr>
<td>Multiple pregnancy rate</td>
<td>0.5%</td>
<td>13.1%</td>
<td></td>
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<tr>
<td>cost reduction</td>
<td></td>
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</tbody>
</table>

*Hum Reprod 2006;21:344–51*
1. **GnRH antagonist protocol**
   
   - GnRH agonist led to ↑ incidence of OHSS: pretreatment blockade of endogenous gonadotropin needs increased dose of FSH for ovarian stimulation
   
   - Rapid competitive blockage of pituitary GnRH receptor ➔ administrated before expected rise in endogenous LH, usually at follicle size 12-14 mm
   
   - Lack of suppression of natural endogenous FSH during early follicular phase ➔ reduced FSH dose for ovarian stimulation
• GnRH antagonist **superior to GnRHa in OHSS rate.**

  *Cochrane Database Syst Rev 2006;(3):CD001750*

  *Hum Reprod Update 2006;12:651–71*

• **Advantages:**
  – Lack of flare effect
  – No accompanying menopausal-like symptoms
  – No refractory period
  – ↓ ovarian cyst formation
  – Shorter treatment cycle
  – ↓ FSH consumption
• GnRH antagonist vs. GnRHa in clinical pregnancy and live birth rate → conflicting
  – Clinical pregnancy rate lower with antagonists.  
    *Cochrane Database Syst Rev 2006;(3):CD001750*
  – No difference.  
    *Hum Reprod Update 2006;12:651–71*

• Further studies indicated.

• **GnRH antagonist regimen** should be considered in normal and predicted high responders.
1. **Avoidance of hCG for LPS**

   - **Luteal phase impairment**: negative feedback of supraphysiological (E2 and P) after hyperstimulation → low endogenous LH → reduced implantation and ↑ pregnancy loss

   - **Luteal phase support**: $P \pm E2$
     - **hCG**: shown to have benefit in agonist cycle but ↑ risk of OHSS
     - **Progesterone**: halve OHSS risk, similar benefit
       
       - *Cochrane Database Syst Rev 2004;(3): CD004830*
       
       - *Fertil Steril 2008;91:1012–7*

     - intranasal GnRHa

1. **In vitro maturation**
   - Offer great potential for OHSS prevention
   - Not widely used due to ↓ live birth rate
   - Clinical outcomes improved in recent years

1. **Insulin-sensitizing agents**
   - Insulin resistance with hyperinsulinemia thought to play a role in PCOS
   - **Metformin**: cheap, effective insulin-sensitizing agent with good safety profile
     - Meta-analysis (8 RCTs): metformin use during OI or IVF with PCOS → no benefit in clinical outcome but *had positive effect on OHSS* (5)
Secondary prevention

1. Coasting: withholding further gonadotropin stimulation and delaying hCG until E2 plateau or ↓
   - Coasting does not eliminate OHSS but may reduce incidence and severity
     
     *Hum Reprod Update 2002;8:291–6*

   - As 1st line intervention for reducing risk and severity of OHSS in over response pts
     
     *Hum Reprod 2001;16:2491–5*

   - insufficient evidence
1. **Reduced dose of hCG:**

- Cornell low dose protocol: hCG dosage according to serum E2 on the day of hCG administration
  - E2: 2000-3000 pg/ml → hCG 3300-5000 IU
  - E2 >3000 pg/ml → coasting until E2 below 3000 pg/ml

- Similar pregnancy outcome but ↓ in early OHSS and severe OHSS
  

- Potentially increase cycle cancellation rate
- No strong evidence
1. **Cryopreservation of all embryos:**

- after oocyte pickup (OPU) → cryopreservation of embryo → thawed and reimplantation when hormone level not elevated

- Early OHSS associated with hCG administration still occur but late or severe form can be avoided

- Disadvantage: success rate of frozen/thawed embryo lower than fresh embryos

- Evidence conflicting !!
  
  • Retrospective or observational study
1. **Cycle cancellation:**
   - Only guaranteed method for preventing early OHSS
   - Physicians reluctant to use in IVF → financial burden of tx and pts’ psychological distress
1. Alternative agents for triggering ovulation:

- long half life of hCG $\rightarrow$ ↑ OHSS
- risk similar for rhCG

a. GnRHa

- Continued GnRHa $\rightarrow$ receptor down regulation and desensitization

- A bolus of GnRHa in gonadotropin only or antagonist cycle $\rightarrow$ surge (flare) of FSH and LH $\rightarrow$ mimic natural midcycle surge of gonadotropin and stimulating ovulation and final oocyte maturation

- BUT gonadotropin level reduced !!!
a. **GnRHa**

- 4/13 (30.8%) triggered with hCG develop moderate or severe OHSS; 0/15 (0) triggered with GnRHa
  
  *Hum Reprod 2006;21:1260–5*

- 10/32 (31.3%) in hCG group had OHSS; none in GnRHa arm

- hCG compared with GnRHa: risk of OHSS (3.79X), moderate/severe OHSS (1.35X)
  
  *Fertil Steril 2008;89:84–91*

- poor reproductive outcome → luteal phase insufficiency (too low circulating endogenous LH)
a. **GnRHa**

- + a small bolus of LH (1500 IU hCG) after GnRHa triggering

- RCT: GnRHa + hCG 1500 IU (35 hrs after triggering) vs. hCG 10000 IU → no difference in live-birth rate

- Retrieval of more mature oocytes (4%) in GnRHa group → beneficial effect of midcycle FSH surge on oocyte maturity

- 1/3 of pts with >14 follicles of 11 mm → but no OHSS seen in GnRHa triggering group
a. GnRHa

- Additional LPS is important !!!!
  - no consensus form

- In oocyte donation cycle: GnRHa triggering widely adopted as LPS disregarded
  - 2077 donor cycle: 13/1031 pts with moderate or severe OHSS in hCG group but no case in GnRHa group

- GnRHa triggering ovulation is a very promising approach for high-risk pts in conjunction with GnRH antagonist-stimulated cycles
  - Optimal LPS required
a. Recombinant LH
   - More closely mimic LH surge than hCG
   - Reduce pregnancy rate, poor cost/benefit ratio
1. **Other strategies:**
   a. **GnRH antagonist salvage**
      • Administration to pts with elevated E2 at risk of developing OHSS may provide interrupting development or progression of condition
   
   a. **Albumin and hydroxyethyl starch (HES)**
      • **Albumin**: *evidence not strong*
        1. major plasma-binding protein, bind to vasoactive agents responsible for OHSS and facilitate their removal
        2. ↑ plasma osmotic pressure → maintain intravascular volume
      • **HES**: cheaper, safer, as 1\textsuperscript{st} line management
1. **Other strategies:**
   a. **Dopamin agonists:**
      - Cabergoline: owning both 1° and 2° prevention (act at VEGF receptor)
      - Effective in reducing but not eliminating OHSS
   a. **Glucocorticoids**
      - Have inhibitory effect on VEGF gene expression
      - Inhibiting vasodilation and preventing ↑ vascular permeability
      - Undesirable side effect
1. **Nonrecommended strategies:**
   a. **Follicular aspiration**
      - limiting OHSS mediator production
      - cost, patient discomfort, invasive procedure
   a. **Aromatase inhibitors**
      - Aromatase catalyzes rate-limiting step in production of estrogen
      - ↓ excessive E2
Limitation

• Retrospective, uncontrolled, small studies
  – Relative rarity of OHSS, very large sample size required to identify meaningful change
  – Potential seriousness → unethical for RCTs
Take home message

• OHSS is a preventable condition

• Evidence-based strategies enable to reduce the incidence and severity of OHSS

• Improved understanding of OHSS pathogenesis and more accurate predictive test should facilitate more individualized IVF protocol to produce optimal ovarian response and minimize occurrence of OHSS.
## Current clinical guidelines and summary of the most recent evidence for OHSS prevention strategies.

<table>
<thead>
<tr>
<th>OHSS prevention strategy</th>
<th>Findings based on current evidence</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreasing exposure to</strong></td>
<td>Chronic low dose (O1); limited ovarian stimulation (O1); mild stimulation; protocol (IVF); no FSH on day of hCG</td>
<td>1b, 2a, 2b, 4</td>
</tr>
<tr>
<td><strong>gonadotropins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GnRH antagonist</strong></td>
<td>Decreases risk of severe OHSS, reduces incidence of OHSS hospital admissions, reduces the need for secondary interventions such as coasting or cycle cancellation</td>
<td>1a</td>
</tr>
<tr>
<td><strong>Reduced dose hCG for</strong></td>
<td>Appears to reduce risk of severe OHSS but large RCTs needed</td>
<td>2a</td>
</tr>
<tr>
<td><strong>triggering ovulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Avoiding hCG for LPS</strong></td>
<td>Approximately half the risk of OHSS with P for LPS vs. hCG</td>
<td>1a</td>
</tr>
<tr>
<td><strong>IVM</strong></td>
<td>Promising, but no data on OHSS prevention available</td>
<td>—</td>
</tr>
<tr>
<td><strong>Insulin-sensitizing agents</strong></td>
<td>Reduces risk of OHSS in women with PCOS undergoing OI or IVF; may reduce risk of moderate/severe OHSS in normal responders</td>
<td>1a, 2a</td>
</tr>
<tr>
<td><strong>Cycle cancellation</strong></td>
<td>Almost eliminates risk of OHSS; in nonsuppressed cycles, ovulation may still occur and ensuing pregnancy could lead to the development of late OHSS</td>
<td>4</td>
</tr>
<tr>
<td><strong>Coasting</strong></td>
<td>Appears to reduce, but not eliminate, the incidence of severe OHSS in high-risk patients compared with expected values; no placebo-controlled RCTs; optimal criteria and protocols remain to be determined</td>
<td>1a</td>
</tr>
<tr>
<td><strong>Alternative agents for</strong></td>
<td>Very significant reductions in incidence of OHSS in high-risk patients compared with hCG</td>
<td>1b</td>
</tr>
<tr>
<td><strong>triggering ovulation:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GnRHa</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Recombinant human LH</strong></td>
<td>Appears to be effective in reducing the incidence of OHSS, but associated with poor outcomes and high costs; not commercially available</td>
<td>1b</td>
</tr>
<tr>
<td><strong>Cryopreservation of all embryos</strong></td>
<td>Insufficient evidence available</td>
<td>1a</td>
</tr>
<tr>
<td><strong>Antagonist salvage</strong></td>
<td>Appears to halt the development of severe OHSS; as effective as coasting</td>
<td>1b</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>Does not appear to be effective</td>
<td>1a</td>
</tr>
<tr>
<td><strong>Hydroxyethyl starch</strong></td>
<td>Appears to reduce the risk of moderate and severe OHSS</td>
<td>1b</td>
</tr>
<tr>
<td><strong>Follicular aspiration</strong></td>
<td>Results are variable and negative drawbacks of this approach not trivial; cannot recommend</td>
<td>1a</td>
</tr>
<tr>
<td><strong>Aromatase inhibitors</strong></td>
<td>No literature on the effects of aromatase inhibitors on incidence or severity of OHSS</td>
<td>—</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td>Superior to placebo at reducing incidence of OHSS in high-risk patients but does not eliminate the risk</td>
<td>1b</td>
</tr>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td>Conflicting results; may be effective when used at an early stage of ovarian stimulation</td>
<td>2a</td>
</tr>
</tbody>
</table>
THANK YOU!