Contemporary approach in OHSS treatment

HUSEYIN GORKEMLI, MD
KONYA N.E. UNIVERSITY
MERAM MEDICAL SCHOOL

TAJEV 2014
Complications of IVF and ovulation induction

Reija Klemetti1,3, Tiina Sevón1, Mika Gissler2 and Elina Hemminki1

1Research on Practices and 2Information Unit, STAKES, National Research and Development Centre for Welfare and Health, Helsinki, Finland
3To whom correspondence should be addressed: STAKES, P.O.Box 220, 00531 Helsinki, Finland. E-mail: rei.klemetti@stakes.fi

- Finland registry: 9,175 IVF cycles
- Severe OHSS:
  - 1.4% per cycle
  - 2.3% per patient (mean 3.3 cycles/pt)

OHSS
HOW COMMON IS IT?
OHSS
HOW COMMON IS IT?

~ 300,000 IVF (Europe 2003)
~ 130,000 IVF (USA 2005)

→ 430,000 IVF cycles reported
→ 6,020 severe OHSS patients from IVF
Table I. Classification of OHSS*. OHSS may be early onset (within 9 days of hCG trigger) or late onset (after 9 days from hCG trigger), with severity as indicated below.

<table>
<thead>
<tr>
<th>Mild OHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal bloating</td>
</tr>
<tr>
<td>Mild abdominal pain</td>
</tr>
<tr>
<td>Ovarian size usually &lt; 8 cm**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate OHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate abdominal pain</td>
</tr>
<tr>
<td>Nausea ± vomiting</td>
</tr>
<tr>
<td>Ultrasound evidence of ascites</td>
</tr>
<tr>
<td>Ovarian size usually 8–12 cm**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe OHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ascites (occasionally hydrothorax)</td>
</tr>
<tr>
<td>Oliguria</td>
</tr>
<tr>
<td>Haemoconcentration haematocrit &gt; 45%</td>
</tr>
<tr>
<td>Hypoproteinaemia</td>
</tr>
<tr>
<td>Ovarian size usually &gt; 12 cm**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critical OHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tense ascites or large hydrothorax</td>
</tr>
<tr>
<td>Haematocrit &gt; 55%</td>
</tr>
<tr>
<td>WCC &gt; 25,000/ml</td>
</tr>
<tr>
<td>Oligo/anuria</td>
</tr>
<tr>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Adult respiratory distress syndrome (ARDS)</td>
</tr>
</tbody>
</table>

*Mathur et al. (2005); see also: http://www.rcog.org.uk for full explanation.

**Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration.
Outline

- Risk factors
- Prevention
- Management
OHSS RISK FACTORS

1. Young age
2. Low BMI
3. PCOS
4. Allergic history
5. High TAFC
6. High doses of gonadotropins
7. High or rapidly rising E2 levels
8. Large number of large & medium-size follicles
9. Large numbers of eggs retrieved
10. High or repeated doses of hCG
11. Pregnancy
12. Previous OHSS
| Estradiol          | Estradiol level is a reliable predictor of OHSS during ART [5]  
|                   | OHSS can occur despite low estradiol levels [10]  
|                   | High estradiol concentrations are not sufficient to induce OHSS [6]  
|                   | Currently considered a mere marker of granulose activity [11]  
| hCG               | Fundamental for triggering OHSS  
|                   | hCG alone is not sufficient to induce OHSS [4]  
| Interleukins      | Some interleukins are associated with OHSS, and elevated concentrations  
|                   | are associated with increased vascular permeability, hemoconcentration,  
|                   | elevated plasma estradiol concentration, and inhibition of hepatic albumin production [12]  
| Renin-angiotensin system | There is a direct correlation between plasma renin activity and the severity of OHSS [13]  
|                   | All hypovolemic conditions are associated with a secondary reactive hyperaldosteronism  
|                   | via renin-angiotensin cascade activation [17]  
|                   | Renin-angiotensin system activation is probably the effect and not the cause of OHSS  
| VEGF              | VEGF expression is associated with OHSS increased vascular permeability [18]  
|                   | VEGF levels are elevated during ovarian stimulation with exogenous FSH, which is  
|                   | enhanced after hCG administration [19, 20] |
OHSS RISK FACTORS

E2 levels are over-rated predictors of OHSS

- A cut-off of 3,000 pg/ml will miss 2/3 of severe OHSS
- Number of follicles ≥ 12 mm better pred. than E2
- E2 ≥ 5,000 and ≥18 foll best predictor of OHSS
  - 83% SENSITIVITY
  - 84% SPECIFICITY

Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles

Evangelos G. Papanikolaou, M.D., Ph.D., Cristina Pozzobon, M.D., Efstratios M. Kolibianakis, M.D., Ph.D., Michel Camus, M.D., Herman Tournaye, M.D., Ph.D., Human M. Fatemi, M.D., Andre Van Steirteghem, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.

Centre for Reproductive Medicine, University Hospital, Dutch-Speaking Brussels Free University, Brussels, Belgium

Which patients become high risk for OHSS during HMG therapy?

1. Those with high serum estradiol concentrations
   When to measure E2? Is there a cut-off value?
   - Day 3-5: Poor sensitivity and high False Pos Rate
     *Hendrics et al 2004*
   - Day 9: E2 > 800pg/ml
   - Day of HCG: E2 > 3000pg/ml
     *Delvigne et al (1997); Navot et al (1998)*
Estradiol concentration on day of HCG and risk for OHSS

Asch et al (1991)

- E2 < 3500 pg/ml    ----------------- 0%
- 3500 pg/ml < E2 < 5999 pg/ml --- 1.5%
- E2 > 6000 pg/ml ------------------- 38%

Sensitivity: 83%   Specificity 99%

Levy et al (1996); Shimon et al (2001);

- OHSS with E2 < 500 pg/ml !!!
  which means 1…2…3…
Estradiol concentration on the day of HCG and risk for OHSS

1. There is a large overlap in E2 concentrations between women who develop and women who do not develop OHSS.

2. E2 concentration is inadequate as the only predictive factor.

3. Is found at highest concentrations >6000pg/ml when it becomes very predictive of OHSS.
Which patients become high risk for OHSS during HMG therapy?

2. Those who have large number of follicles on the day of HCG
   - >14 follicles of 11mm. (Papanikolaou et al 2006)
   - >11 follicles of 10mm. (Lee et al 2008)

3. Those who have large number of oocytes retrieved
   - >30 OOR 14% severe OHSS (Morris et al 1995)
   - <20 0% severe OHSS (Asch et al 1991)
   - <20 OOR < 30 1.4% severe OHSS
   - >30 OOR 23% severe OHSS
The role of VEGF in OHSS

- OHSS is a dramatic complication of OI
- VEGF mRNA is expressed by granulosa & theca cells
- Ovarian VEGF levels correlate with the dose of gonadotrophins administered
- Excess of bioactive VEGF in FF increases OHSS risk
- VEGF expression is dependent on LH
- There is an association between hCG & OHSS
- VEGF is increased by hCG in a dose- & time-dependent fashion

*Rizk B et al, HR Update. 1997; (3): 255-66*
*Neulen J et al, Hum Reprod, 2001; 16(4): 621-6*
*Gomez et al, Bio Repro 2003*
PCO - high risk for OHSS
OHSS - AMH

- >1.26 ng/ml normoresponder
- >3.36 ng/ml OHSS risk
- >7 ng/ml OHSS risk very high
OHSS PREVENTION STRATEGIES
CAREFUL CLINICAL APPROACH

BEFORE STIMULATION
1. Use protocols with low dose HMG
2. Use protocols that reduce the duration of exposure to HMG
3. GnRH Antagonists
4. Insulin Sensitizers
5. IVM of Oocytes

DURING STIMULATION
1. Low D HCG to trigger Ov/tion
2. GnRHa to trigger Ov/tion
3. Recombinant human LH
4. Coasting
5. Cycle cancellation
6. Cryopreservation of embryos
7. IV Albumin
8. Hydroxyethyl starch
9. Glucocorticoids
10. DOPAMINE AGONISTS
Prevention OHSS

A. Cancel Cycle - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis
Non-IVF cycles

- **Recommended Stimulation Protocols with Low Dose HMG**

1. Low dose step-up protocol
   75IU FSH -- 37.5IU
   *(Homburg and Howels 1999)*

1. Step-down protocol
   150IU FSH – 75IU
   *(Macklon and Fauser 2000)*
In IVF cycles

- **Recommended Stimulation Protocols with Low Dose HMG**

1. Limited Ovarian Stimulation (LOS) protocol-PCO
2. HMG stimulation until the leading follicle reached 12mm prior to HCG (El-Sheikh et al 2001)
3. Low starting dose of 150IU FSH for all patients at high risk for OHSS (Homburg and Insler 2002)
4. FSH from day5+GnRHant when follicles >/=14 (Hobmann et al 2003)
PREVENTION OHSS

A. **Cancel Cycle** - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis
PREVENTION OHSS

*Cancel Cycle – withhold hCG trigger*

- **IVF:** Most effective preventative technique, BUT emotionally & financially stressful
- Reserved for prior severe OHSS and total loss of control of the cycle
PREVENTION OHSS

A. Cancel Cycle - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis
PREVENTION OHSS

Coasting

CONCEPT: Stopping gonadotropin and postponing hCG trigger until E2 level is lower.

Mechanism

- Lower gonadotropin stimulation → decreased LH receptors → decreased luteinization → ↓ VEGF
- Lower gonadotropin stimulation may increase rate of granulosa cell apoptosis, especially of smaller follicles
- Coasting lowers concentration of follicular fluid VEGF

PREVENTION OHSS

Coasting

What does the literature tell us:

- Unable to determine true effectiveness of coasting since no RCT
- Indications for coasting variable amongst studies
- Target E2 level quite variable (typically about 3,000 pg/ml)
- Coasting does not totally prevent OHSS: 16% of patients still had ascites and 2.5% required hospitalizations\(^1\)
- Coasting for > 4 days results in lower pregnancy/implantation rates\(^2,3\)

PREVENTION OHSS

A. Cancel Cycle - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis
PREVENTION OHSS

*Decrease dose of hCG*

Reducing the dose of human chorionic gonadotropin in high responders does not affect the outcomes of in vitro fertilization

David W. Schmidt, M.D., Donald B. Maier, M.D., John C. Nulsen, M.D., and Claudio A. Benadiva, M.D.
The Center for Advanced Reproductive Services, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Connecticut Health Center, Farmington, Connecticut

<table>
<thead>
<tr>
<th>OHSS</th>
<th>5,000 IU</th>
<th>3,300 IU</th>
<th>P value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10.6% (5/47)</td>
<td>21.3% (10/47)</td>
<td>.357</td>
</tr>
<tr>
<td>Mild</td>
<td>8.5% (4/47)</td>
<td>6.3% (3/47)</td>
<td>.978</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.1% (1/47)</td>
<td>10.6% (5/47)</td>
<td>.207</td>
</tr>
<tr>
<td>Severe</td>
<td>0% (0/47)</td>
<td>4.2% (2/47)</td>
<td>.495</td>
</tr>
</tbody>
</table>

*Not significant.


Retrospective review of high responders

- 94 IVF cycles
- If E₂ 2,500-4,000 pg/ml → 5,000 IU hCG
  E₂ > 4,000 pg/ml → 3,300 IU hCG

RESULTS

- No difference in OHSS but note excellent maturation with as low as 3,300 IU hCG
PREVENTION OHSS

Decrease dose of hCG

Triggering final oocyte maturation using different doses of human chorionic gonadotropin: a randomized pilot study in patients with polycystic ovary syndrome treated with gonadotropin-releasing hormone antagonists and recombinant follicle-stimulating hormone

Efstathios M. Kolibianakis, M.D., Ph.D., Evangelos G. Papanikolaou, M.D., Ph.D., Herman Tournaye, M.D., Ph.D., Michel Camus, M.D., Andre C. Van Steirteghem, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.

Centre for Reproductive Medicine, Vrije Universiteit Brussel, Brussels, Belgium

SAME DEAL……..

Although it theoretically makes sense to reduce the dose of hCG, there is little data to support.

Studies are small/not powered to detect a difference.

<table>
<thead>
<tr>
<th>Trigger</th>
<th>10,000 IU</th>
<th>5,000 IU</th>
<th>2,500 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Preg</td>
<td>26.9%</td>
<td>30.8%</td>
<td>34.8%</td>
</tr>
<tr>
<td></td>
<td>7/26</td>
<td>8/26</td>
<td>8/23</td>
</tr>
<tr>
<td>Severe OHSS</td>
<td>1/26</td>
<td>1/26</td>
<td>0/26</td>
</tr>
</tbody>
</table>

Article

Low-dose HCG is useful in preventing OHSS in high-risk women without adversely affecting the outcome of IVF cycles

Abstract

Severe ovarian hyperstimulation syndrome (OHSS) is a rare but potentially fatal condition associated with conventional IVF treatment. It is found predominantly in women with polycystic ovaries who have an exaggerated response to exogenous FSH, leading to a large number of follicles and an overproduction of vascular endothelial growth factor with resultant excessive increases in vascular permeability. There is evidence to suggest that OHSS is also linked to the use of human chorionic gonadotrophin (HCG) to induce ovulation. Therefore while HCG is essential for corpus luteum function, high amounts of HCG can lead to OHSS in high responders. In a pilot study, infertile patients at high risk of developing OHSS were given half the current minimum dose of HCG (i.e. 2500 IU). No woman developed moderate or severe OHSS; 13 women (61.9%) conceived and there were three twin pregnancies. In women at high risk of OHSS, a low dose of HCG appears to prevent the development of OHSS without compromising success rates.
PREVENTION OHSS

A. Cancel Cycle - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. **Agonist trigger**
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis
PREVENTION OHSS

Agonist trigger

- Reserved for antagonist protocol
- Agonist (Triptorelin 0.2 mg, Lupreulide 1 mg) trigger
- First described by Itskovitz-Eldor J et al (Hum Reprod 2000) to treat 8 patients at risk for OHSS

- So, what’s the data……………….
PREVENTION OHSS

**Agonist trigger**

GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis

G. Griesinger, K. Diedrich, P. Devroey, and E. M. Kolibianakis

1 Department of Obstetrics and Gynecology, University Clinic of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany and 2 Centre of Reproductive Medicine, Dutch Speaking, Brussels Free University, Brussels, Belgium

To whom correspondence should be addressed at: Ratzeburger Allee 160, 23538 Luebeck.
E-mail: georg.griesinger@frauenklinik.uni-luebeck.de

- 23 papers published
- Only 3/23 meet criteria for meta-analysis (RCT)

**Agonist versus hCG Trigger**

- No diff in no. oocytes, fert rate, or embryo score
- No OHSS either gp

**BUT**

- Lower preg rate with agonist trigger
  (? Lut support issue)
Comparison of GnRH agonists and antagonists in assisted reproduction cycles of patients at high risk of ovarian hyperstimulation syndrome

G.Ragni$^{1,4}$, W.Vegetti$^1$, A.Riccaboni$^1$, B.Engl$^2$, C.Brigante$^3$ and P.G.Crosignani$^1$

...fer) were obtained. CONCLUSIONS: Although this study presents some limitations owing to the use of historical controls, our data show a favourable effect of GnRH antagonists in reducing the incidence of OHSS and the number of assisted fertilization cycles cancelled because of the risk of OHSS in high responder patients. As a consequence, GnRH antagonist plus gonadotrophin administration could also increase the percentage of oocyte...

**Figure 1.** Comparison of stopped cycles, oocyte retrieval, embryo transfer and incidence of OHSS between the two treatment cycles (filled bars, GnRH agonist; empty bars, GnRH antagonist). Values are expressed in percentages; differences were statistically significant for stopped cycles and oocyte retrieval (both $P < 0.001$), embryo transfer ($P < 0.003$) and OHSS ($P < 0.006$).
PREVENTION OHSS

A. Cancel Cycle - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis
PREVENTION OHSS

Cryopreservation of all embryos

OHSS is more common and severe with pregnancy due to hCG-induced ovarian stim.

THE DATA

✓ Cochrane review found insufficient evidence
  
  *Amso NN, D’Angelo (2002) Hum Reprod*

✓ As with all methods, it may reduce but not eliminate OHSS
  
  *Queenan Jr JT (1997) Hum Reprod*

✓ Cryo = Coasting
  
  *Benavida C et al. (1997) F&S*

✓ Cryo = IVF albumin
  
  *Shaker A (1996) F&S*
PREVENTION OHSS

A. Cancel Cycle - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. **IV albumin at time of egg retrieval**
G. Paracentesis
PREVENTION OHSS

IV Albumin prophylaxis

Intravenous albumin does not prevent moderate-severe ovarian hyperstimulation syndrome in high-risk IVF patients: a randomized controlled study

José Bellver¹, Elkin A. Muñoz, Agustín Ballesteros, Sérgio Reis Soares, Ernesto Bosch, Carlos Simón, Antonio Pellicer and José Remohí

Department of Infertility, Instituto Valenciano de Infertilidad (IVI), Plaza de la Policía Local 3, 46015, Valencia, Spain

¹To whom correspondence should be addressed at: Instituto Valenciano de Infertilidad, Plaza de la Policía Local 3, 46015, Valencia, Spain. E-mail: jbellver@seco.es


Largest/best RCT (976 patients)
- Patients at high risk OHSS (20 eggs)
- 40 g albumin at VOR versus nothing x 30 minutes

CONCLUSIONS
- No benefit of albumin
- Risks (prions, virus/CJD

Table IV. Comparison of clinical evolution of albumin and control groups in severe ovarian hyperstimulation syndrome (OHSS) cases (n = 46)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albumin group (n = 23)</th>
<th>Control group (n = 23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracentesis (n)</td>
<td>21</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>No. of paracenteses per patient</td>
<td>1.3 (0.8)</td>
<td>1.9 (1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital admission (n)</td>
<td>7</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Complications (n)</td>
<td>3ª</td>
<td>2ª</td>
<td>NS</td>
</tr>
<tr>
<td>Days from oocyte retrieval to beginning of OHSS</td>
<td>4.4 (4.0)</td>
<td>4.5 (3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of OHSS (days)</td>
<td>8.4 (5.8)</td>
<td>10 (6.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise indicated.
³Two adult respiratory distress syndromes and one pleural effusion.
³One thromboembolic event and one cerebrovascular accident.
Dopamine Agonist Cabergoline Reduces Hemoconcentration and Ascites in Hyperstimulated Women Undergoing Assisted Reproduction
PREVENTION OHSS

A. Cancel Cycle - withhold hCG trigger
B. Coasting
C. Decrease dose of hCG trigger
D. Agonist trigger
E. Cryopreservation of embryos
F. IV albumin at time of egg retrieval
G. Paracentesis
Outpatient paracentesis

**STUDY RESULTS**

- 146 outpatient paracentesis (96 patients)
  - 50 pts (52%) → Only one paracentesis
  - 35 pts (36%) → paracentesis #2
  - 8 pts (8%) → paracentesis #3
  - 3 pts (3%) → paracentesis #4
  - 1 pt (1%) → paracentesis #5

- Volume of fluid removed
  - Mean: 2,155 ml
  - Range: 500-4,500 ml
Prevention of OHSS

1. Coast when E2 levels very high or too many medium range follicles
2. Always give standard dose of hCG (Ovidrel®) - Never cancel cycle irrespective of E2
3. No IV albumin prophylaxis
4. Cryo-all if patient is symptomatic on day of ET
5. Aggressive outpatient vaginal paracentesis for moderate-severe symptoms.
SUMMARY
Prevention of OHSS

- No universally agreed upon best method to prevent OHSS
  - Coasting the most common method used, followed by cryopreservation of embryos
  - Consider outpatient paracentesis early!

- Data limited in RCT for all preventative measures
  - Difficult to prove on method superior due to low incidence of severe OHSS
Summary points

1. OHSS is a potentially life threatening complication
2. Estradiol levels alone not highly predictive
3. Beware of risk factors
4. The only method to completely prevent OHSS is cycle cancellation.
5. No good data on best method to prevent OHSS (due to ↓ incidence)
6. Not totally preventable although coasting and freezing embryos are most commonly used.
7. Outpatient paracentesis prevents hospitalizations.
## OHSS Prevention Strategies

**Summary**

#### Effective
- Low dose HMG
- GnRH ant
- Metformin (PCO)
- IVM
- Low dose HCG
- GnRHag to trigger ovulation
- Coasting
- HES
- Dopamine agonists

#### Not Effective/Doubtful
- Recombinant LH
- IV Albumin
- Cryopreservation

*Dr. Lukas D. Klentzeris*
Thank you for your patience…