Ovarian hyperstimulation syndrome: OHSS: can we prevent it, and can we treat it?

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There are no commercial relationship or other activity related to this lecture which might be perceived as a potential conflict of interest.
Learning Objectives

At the conclusion of this course, the participant should be able to:

1. Detect the prevalence and predisposing factors of OHSS
2. Discuss the efficacy of each preventive measure of OHSS
3. Summarize the different measures to prevent OHSS
4. Discuss lines of treatment of OHSS.
OHSS is the most serious complication of ovulation induction.

In its severest forms, it is complicated by hemoconcentration, venous thrombosis, electrolyte imbalance and renal and hepatic failure

(Schenker and Weinstein 1978; Navot et al. 1992; Aboulghar et al. 1993)
How to prevent OHSS?

1. Identifying patients at risk before ovulation induction.
2. Low dose FSH / hMG
3. GnRH antagonist protocol
5. Metformin
6. Patients at risk during ovulation induction:
   • Canceling the cycle
   • Coasting
   • GnRH antagonist
   • hCG dose and alternatives
   • Cryopreservation of all embryos
   • Albumin / starch
   • Dopamin agonist
   • Triggering ovulation by GnRHa
First

Identifying patients at risk before ovulation induction:

• History of previous OHSS
• PCOS patients are more liable to develop OHSS

(Schenker and Weinstein 1978; Navot et al. 1992; Bider et al. 1989; Rizk et al. 1992; Aboulghar et al. 1992)
PCOS patients are more liable to develop OHSS:

1- Oligomenorrhea or periods of amenorrhea

2- Hormonal profile (FSH/ LH), high LH, high AMH (Aboulghar et al. in press)

3- Ultrasonography
   • Increased ovarian volume (Danning et al. 1996; Lass et al. 2000)
   • Number of antral follicles and necklace appearance (Navot et al. 1992)

5- Young age < 35 years old (Navot et al. 1992)

6- Lean body (Asch et al., 1991; Ayhan et al., 1996)
Stimulation protocols for non IVF cycles

• Low dose step-up protocol
  – (Homburg and Howles, 1999)
  – 225 women with PCO stimulated by low dose protocol for 934 cycles resulted in 109 pregnancies, 7 twin pregnancies and no OHSS (White et al. 1996).
Stimulation protocols for IVF cycles

- Lower doses of gonadotrophins \((Homburg \text{ } \text{and} \text{ } \text{Insler} \text{ } 2002)\)

- GnRH agonist protocol increases the incidence of OHSS \((Rizk \text{ } \text{and} \text{ } \text{Smitz} \text{ } 1992)\).

- GnRH antagonist protocol \((Al-Inany \text{ } et \text{ } al \text{ } 2011)\).
**Meta-analyses Confirm That GnRH Antagonists Have a Better Safety Profile vs GnRH Agonists**

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<th>Kolibianakis</th>
<th>Al-Inany</th>
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<tbody>
<tr>
<td><strong>Risk of severe OHSS</strong></td>
<td>RR 0.46* (0.26, 0.82; (P=0.01))</td>
<td>OR 0.61 (0.42, 0.89; (P=0.01))</td>
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<tr>
<td><strong>Interventions to prevent OHSS</strong></td>
<td>OR 0.44 [0.21, 0.93] vs. agonist; (P=0.03)</td>
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*For every 59 women treated with a GnRH agonist vs GnRH antagonist, one additional case of severe OHSS will occur.

OR = Odds ratio; RR = Risk ratio

Low Gonadotropin doses

Starting with 150 IU for all patients at a possible risk irrespective of age is recommended (Golan et al., 1988; Homburg and Insler 2002; El-Sheikh et al., 2001)

Type of gonadotropins: Urinary or Recombinant

No significant difference in the occurrence of OHSS (van Wely et al. et al., 2003)
Careful monitoring of ovarian response to diagnose patients at risk

1. **US:**
   - *PCOS pattern*
   - *Large number of follicles*
   - *Increase in the fraction of very small follicles and decrease in the fraction of dominant follicles* (Blankstein et al 1987)

2. **E2**
   - *Log E2 and Slope E2 increment was a good predictor to OHSS* (Delvigne et al 1993)
Patients at risk of OHSS during ovulation induction using GnRH-a protocol

I. Stop hMG and continue down regulation. (Complete prevention) (Nardo et al. 1992; Rizk and Aboulghar, 1999; Aboulghar and Mansour 2003)

II. Coasting.

III. GnRH antagonist.
Withholding hCG and cycle cancellation

• After the introduction of other different modalities for prevention of OHSS in high risk patients and in particular coating, withholding hCG with cyclic cancellation is seldom used (Orvieto 2005).
Cryopreservation of all embryos: a Cochrane review

When elective cryopreservation of all embryos was compared with fresh embryo transfer no difference was found between the two groups. However severe forms of OHSS may develop if pregnancy occurs. (D’Angelo and Amso (2002))
Coasting

It is stoppage of FSH stimulation and monitoring of E2 level
Coasting

• Coasting for non-IVF cycles.
  • Rabinovici et al., (1987)
Coasting for IVF cycles

- Sher et al., (1993) suggested that prolonged coasting in GnRH-a/hMG.FSH cycles could prevent live-endangering complications of OHSS.

- Sher et al., (1995) treated 51 women at great risk of developing OHSS by coasting until the plasma E2 fell to <3000 pg/ml. There were 21 clinical pregnancies (41%/oocyte retrieval). None of the women developed severe OHSS.
Coasting

• When to start coasting:
  When the mean diameter of the follicles reaches 16 mm and the E2 level is above 3500 pg/ml (Mansour et al 2005).
What happens when you start coasting?

• Follicular growth will continue with the same rate.
• E2 will continue to rise then will platform and then decline.
Mature follicles can survive for a few days without exogenous FSH/hMG while small follicles will undergo apoptosis / necrosis

(Garcia-Velasco et al., 2004)
Coasting diminishes the granulosa cell cohort

In the absence of gonadotropin stimulation, dominant follicles will continue their growth, while intermediate and small ones will undergo atresia.
How to monitor coasting cycles?

- Daily E2 assays.
- Daily folliculometry.

When to give hCG

When E2 levels drop to 3000 pg/ml
Problems with coasting

• Occasionally E2 drops markedly to very low levels and cycle is canceled.
• Difficulty in identification of oocytes in aspirated follicular fluid after prolonged coasting.
Are there specific Lab precautions?

Yes

Extra time and care is needed in order to find the oocytes due to the diminished amount of granulosa cells
The experience of the Egyptian IVF Center (Mansour et al. 2005)

• From January 2000 till December 2004, 12,494 ICSI/IVF cycles were performed at the Egyptian IVF-ET Center. Coasting was done for 1223 patients that were diagnosed to be at risk of developing OHSS during that period.
## ICSI outcome according No. of coasting days

<table>
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<tr>
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<th>Group I up to 3 days</th>
<th>Group II 4 days or more</th>
<th>P-value</th>
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<tr>
<td>Cycles</td>
<td>983</td>
<td>240</td>
<td></td>
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<tr>
<td>E2 level on day of hCG (pg/mL)</td>
<td>2674±1789</td>
<td>2801±1930</td>
<td>P=0.88</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>16.45±6.26</td>
<td>14.93 ±6.01</td>
<td>P=0.002*</td>
</tr>
<tr>
<td>MII oocytes</td>
<td>12.94 ±5.58</td>
<td>11.6 ±5.61</td>
<td>P=0.003*</td>
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<tr>
<td>Fertilization rate</td>
<td>62.67%</td>
<td>64.92%</td>
<td>P=0.06</td>
</tr>
<tr>
<td>Embryo per transfer</td>
<td>2.99 ±0.69</td>
<td>3.03 ± 0.66</td>
<td>P=0.27</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>26.32%</td>
<td>18.16%</td>
<td>P=0.0001*</td>
</tr>
<tr>
<td>Clinical PR</td>
<td>51.96%</td>
<td>35.88%</td>
<td>P=0.0002*</td>
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Severe OHSS occurred in 16 cases which is 0.13% (16/12,494) of stimulated cycles as compared to 1.8% in our report before introducing coasting (Aboulghar et al 1993) and 1.3% (16/1223) of patients at risk of developing OHSS who underwent coasting (Mansour et al., 2005)
GnRH antagonist during stimulation of high risk patients

Forty-seven patients at high risk for OHSS because of markedly elevated E₂ were treated with ganirelix acetate. Despite being pretreated with GnRH agonist and without withholding gonadotropins, serum E₂ decreased by 49.5% of pretreatment value after initiation of ganirelix, and 68.1% of the patients became pregnant (Gustofson et al 2006).
Antagonist for prevention of OHSS
Aboulghar et al 2007

190 patients at risk for OHSS

94

GnRH antagonist administration

96

Coasting

No cases of OHSS in both arms

-Significantly more high quality embryos
-Significantly less days than coasting
Metformin and IVF in PCOS patients a Cochrane review (TSO et al 2009)

- No evidence that metformin improves pregnancy or live birth rate.
- Metformin significantly reduces OHSS rates (OR 0.27, 95% CI 0.16-0.47)
IV albumin for prevention of OHSS: A Cochrane review

IV albumin does not significantly reduce the incidence of OHSS (Youssef et al 2011).
Dopamine agonist in prevention of OHSS
Cabergoline was administered in 20 women at risk of OHSS. No OHSS developed in all patients. The authors believe that the drug may be even more effective if administered immediately after oocyte retrieval. Cabergoline may work through the relation between VEGF/VEGFr and its relation with the neurotransmitter dopamin (Manno et al 2004).
Cabergoline reduces early onset of moderate OHSS: a randomized study
(Carizza et al 2008)

83 patients

Cabergoline 0.5 mg
For 3 weeks

83 patients

No TT

Cabergoline reduces the incidence of early OHSS.
A larger study on high risk patients is required
(Alvarez et al 2007)
• In a Cochrane review (Tang et al 2012) which included two studies showed that cabergoline reduces the incidence of moderate OHSS and it does not affect pregnancy outcome.
Triggering ovulation and OHSS

- Reducing the hCG trigger dose. (Abdalla 1987)
- The use of recombinant hCG to trigger ovulation. (Driscoll et al 2000)
- Recombinant LH for triggering ovulation.
- Gonadotrophin releasing hormone agonist to trigger ovulation.
• In a meta analysis of three studies comparing triggering ovulation in antagonist cycles, it was found that GnRHa triggering is associated with significantly lower OHSS rate and also lower ongoing pregnancy rate as compared with triggering with hCG (Griesinger et al 2006).
• Several non-randomized studies suggest that trigger ovulation with GnRHa supplement with small doses of hCG or high doses of progesterone can result in a similar pregnancy rate as hCG triggering (Humaidan et al 2012, Humaindan 2012, Kol et al, 2011).
Treatment of OHSS
Management of moderate OHSS

• Follow up by regular telephone calls and office visits.

• Instructions for patients to report to hospital if she develops dyspnea, or if volume of urine is diminished or upon development of any unusual symptoms.
Management of severe OHSS with normal biochemical profile (Grade A)

Outpatient basis
Aboulghar et al 1993
Shrivastav et al., 1994

• IV 1-3 litres of fluid.
• IV albumin.
• Aspiration of ascitic fluid.
• Day care was simple, safe and effective and avoided hospitalization.

Hospitalization

Observation
Management of severe OHSS with abnormal biochemical profile (Grade B)

Clinical monitoring

- Vital signs.
- Daily weight gain.
- Abdominal Girth measurement.
- Urine output.
Management of severe OHSS monitoring (cont.)

- Hematocrete
- Plasma and urine osmolarity and electrolytes.
- Creatinine and electrolytes.
- Clotting parameters.
- Tests for thrombophelia.
- Liver function tests.
- BHCG.
- Chest, abdomen and pelvic Sonography.
- Chest X-ray.
Correction of circulatory and electrolyte imbalance

1. Aggressive monitoring, e.g. CVP in critical cases.
2. Correction of electrolyte imbalance.
Drugs in treatment of OHSS

• **Anti coagulant therapy:**
  - It is believed that prophylactic heparin should be given for long periods to all patients with severe OHSS (stewart et al 1997; Aboulghar et al., 1998).
  - Full heparization in established cases of thrombosis.
Drugs in treatment of OHSS

Dopamine has been used in oliguric patients with severe OHSS resulting in significant improvement in renal function and increasing renal blood flow and glomerular filtration, however dopamine therapy should be given continuously and used under strict observation (Ferraretti et al 1992).
Drugs in treatment of OHSS

Docarpamine an oral dopamine prodrug, 750 mg orally tds improved clinical symptoms and promoted diuresis in 19 out of 22 patients with no major adverse effects (Tsunoda et al 2003).
Drugs in treatment of severe OHSS

• Diuretics:
  – Diuretic therapy may prove detrimental by further contracting the intravascular volume, increased blood viscosity and increase risk of thrombosis. It may be given in patients who develop pulmonary edema (Rizk and Aboulghar 2005).
GnRH antagonist for treatment of early OHSS (Lainas et al 2009)

- In 3 patients with severe early OHSS, GnRH antagonist was given daily for a week, symptoms subsided and embryos were cryopreserved at blastocyst stage for future ET.
Abdominal paracentesis

• Indwelling peritoneal catheter, introduced by ultrasound guidance and left for continuous drainage. (Abuzeid et al. 2003)
Ultrasonographically guided vaginal aspiration of ascites in the treatment of severe OHSS

(Aboulghar et al. prospective randomized study, 1990)

<table>
<thead>
<tr>
<th></th>
<th>No aspiration</th>
<th>Aspiration</th>
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<tbody>
<tr>
<td>Severe symptoms</td>
<td>9 days</td>
<td>Immediate improvement</td>
</tr>
<tr>
<td>Average hospital stay</td>
<td>11 days</td>
<td>4 days</td>
</tr>
<tr>
<td>Urine outcome</td>
<td>Oliguria</td>
<td>Diuresis</td>
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</table>
In a large study of 42 severe OHSS patients, clinical and biochemical parameters improved after aspiration and IV fluid therapy.

Aboulghar, et al. 1993
Intensive IV fluid therapy combined with transvaginal aspiration of ascitic fluid resulted in a dramatic increase in renal output, decrease in hematocrit, and marked immediate improvement of symptoms and blood chemistry.
How does it work?

• Relieves the intra-abdominal pressure.
• Increases venous return.
• Improves renal perfusion.
• Other mechanisms?
In this large series of OHSS including some critically ill patients, no venous thrombosis, embolism or renal shutdown was reported.
Surgery

• Only in:
  - Hemorrhage.
  - Torsion.
  - Rupture.
  - Ectopic.

• Only haemostatic.
Conclusions

The most effective measures in preventing OHSS:

I. Identifying patients at risk of developing OHSS before ovulation induction:

* Previous history of OHSS
* PCOS
Conclusions (cont.)

II. Low doses of hMG

III. Patients during ovulation induction and at risk of OHSS:

1- Coasting

2- GnRH antagonist protocol

3- hCG 5000 IU only to trigger ovulation
Conclusions (cont.)

4- GnRH agonist to trigger ovulation

5- Progesterone only for luteal phase support

6- Other Measures:
   - Cycle cancelation
   - Cryopreservation of all embryos: There is insufficient evidence for its value.
   - IV albumin or Starch: No evidence of beneficial effect.
   - Dopamin agonist
   - Metformin
Conclusions (cont.)

7. Moderate OHSS should be treated conservatively.

8. Severe OHSS is treated by hospitalization, monitoring and IV albumin and fluid therapy.

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