OHSS - Have we found a solution?

YES

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Serious and detrimental complication of ART due to

- Ovarian stimulation
- HCG used for triggering

**Ovarian hyperstimulation syndrome**

Pathophysiology

- LH/hCG receptors
- hCG
- Granulosa cells
- Endothelial cells
- Monocytes
Incidence and risk factors

All women undergoing COS should be considered potentially at risk of OHSS

Mild to Moderate OHSS - 0.6 to 14% of 'conventional' IVF cycles

Severe OHSS 0.2-0.5%

Incidence in 'modified' and 'mild' stimulation protocols is unknown, but likely to be lower

PCOS
Excessive ovarian response
Younger women < 30 years
Low BMI

High GT dose for OI
Increased hCG exposure - LPS with hCG and MP

Previous OHSS

Mozes, Lancet 1965
García Velasco & Pellicer, 2002
Risk factors

Prior AMH level at cut off 3.36 ng/ml
Sensitivity of 90.5%
Specificity of 81.3%

Blood group A associated with early-onset OHSS, putatively via elevated VWF and factor VIII

Rapidly increasing E2 levels of > 75% from previous day
E2 > 3500 pg/ml on day of hCG

Optimum Cut off value for AFC = >14
Sensitivity 82%
Specificity 89%

Occurrence of pregnancy

> 20 oocytes retrieved
**PATHOPHYSIOLOGY**

**Increased vascular permeability**

**Arteriolar vasodilation**

**Ovarian enlargement**

**VEGF**

**Ang-2**

**Ang-1**

**Tie-2**

**Cadherina-VE**

**VEGFR-2**

**MAIN CLINICAL FEATURES**

**Ascites**

**Intravascular dehydration**

**SEQUELAE**

- **Thromboembolism**: 1 - 10%
- **Renal dysfunction**: 30%
- **ARDS**: 10 - 12%
- **Liver dysfunction**: 25%
OHSS - classification of severity

**Mild**
- Abdominal bloating
- Mild pain
- Ovaries <8 cm

**Moderate**
- Moderate abdominal pain
- Nausea
- Diarrhoea
- Ultrasound evidence of ascites
- Ovaries usually 8 - 12 cm

**Severe**
- Clinical ascites
- Hydrothorax
- Haemoconcentration (Hct >45%, WBC >15,000/ml)
- Oliguria, Liver dysfunction
- Ovaries usually >12 cm

(Mathur et al 2005, modified from Navot et al 1989)
In its severest form, may have serious impact on the patient's health cause severe morbidity and even mortality
Late OHSS is more likely to be severe than early OHSS

Early (n=48)

- Mild
- Moderate
- Severe

Late (n=30)

- Mild
- Moderate
- Severe

p<0.0001

Late OHSS is more difficult to predict from ovarian response

Mathur et al., 2000 Fertil Steril 73, 901-12
Prevention of OHSS

Identify high risk patients and cycle

Use low risk treatment

Specific measures in individual cases
Early OHSS
Ovarian response
3–9 days

Late OHSS
Pregnancy
10–17 days

Lyons et al. 1994; Mathur et al. 2000
Caution is indicated when any of the following indicators for increasing risk of OHSS are present during COS:

- The emergence of large number of small and intermediate sized follicles (10–14 mm) on USG
- Presence of > 8 – 10 dominant follicles
- Enlarged ovaries
- Presence of free fluid in POD
- Rapidly rising serum E2 levels
- E2 > 3500 pg/ml on day of hCG
Use of Low risk Treatment

- Use of GnRH antagonist instead of GnRH agonist
- Recombinant human LH for trigger
- Administration of lower dose or recombinant hCG
- GnRH agonist trigger in antagonist cycle

Mild Ovarian Stimulation
Experience with OI therapy and recognition of risk factors for OHSS

Highly individualized OI regimens carefully monitored with USG and E2

Use of minimum dose and duration of GT therapy necessary to achieve the therapeutic goal

Key to prevention of OHSS

Gonadotropin Administration
Lower oocyte numbers and E2 concentrations may be surrogate markers of a lower risk of OHSS

GnRH antagonist vs agonist

2.1% vs 3.3%

Cochrane Meta-analysis shows a reduced incidence and interventions for OHSS with antagonist vs agonist (Al-Inany et al 2006)

Potential for using GnRH agonist triggering of ovulation which has lower OHSS risk than hCG trigger

Fertil Steril
Fertil Steril
Administration of lower dose of hCG

- hCG 2500 - 5000 IU as against standard 10000 IU or Rec-hCG 250mcg instead of 500 mcg

- 250 mg rhCG and 5000 IU hCG produced comparable results

- Significantly lower successful oocyte recovery in patients who received 2000 IU hCG
  *Abdalla et al., 1987*

- PR, IR and OHSS rate were similar with urinary and recombinant hCG
  *Driscoll et al., 2000; The European Recombinant Human Chorionic Gonadotrophin Study Group, 2000; Chang et al., 2001*
5000 – 30000 IU up to 10000 IU safe

Effective in inducing final follicular maturation and early luteinization and was comparable with 5000 IU urinary hCG

Resulted in a highly significant reduction in OHSS as compared to hCG

Shoham Z, Schacter M, Loumaye E, Weissman A, Macnamee M, Insler V
Substitution of hCG by single GnRH agonist bolus is the safest protocol and avoids cycle cancelation.

GnRha SC in cycles not involving previous DR with long agonist protocols or when GnRH antagonist used.

Excellent results obtained with egg or embryo vitrification.

Avoid both early- and late-onset OHSS, while eliminating the need for adequate and specific luteal support.

(Kuwayama et al., 2005; Cobo et al., 2008)

Single GnRH agonist injection resulted in combined LH & FSH surges lasting 24 h.

Gonen et al., 1990
GnRH agonist for triggering of ovulation

Most commonly used GnRHa triggering doses:

- Buserelin 0.5mg s.c
- Triptorelin 0.2mg s.c
- Leuprolide 1mg s.c
LH surge: GnRHa vs natural

GnRHa
20-24 h

- Shorter ascending phase
- Shorter plateau

Natural
36-48 h

- Longer decending phase

Additional FSH surge
- Induce LHR in GC
- Promote oocyte nuclear maturation
- Cumulus expansion
- Suppression of intercellular coupling of cumulus cells

Hoffer, 1983; Gonen, 1990; Itskovitz, 1991
Massive and irreversible luteolysis after GnRHa trigger

Completely prevents early onset OHSS

Endogenous LH surge with short half-life results in defective CL development and significantly reduced total amounts of LH and FSH

Segal and Casper, 1992

Direct effect on endometrial receptivity

Administration of GnRh agonist instead of hCG for trigger
Administration of GnRH agonist instead of hCG for trigger

More physiological
Endogenous FSH surge
Steroid level in luteal phase closer to physiological condition
LP impacted severely by COS - So remove ovarian stimulation and then——?

hCG increase LH activity but does not reconstitute the midcycle physiologic FSH surge
Causes rise in intrafollicular P4
Development of multiple corpora lutea

T1/2 endogenous LH shorter for GnRHα - 20 mins as against 33 hours with hCG

Simpler cycle monitoring with less or no E2 assay
No coasting or cycle cancellation

More MII oocytes harvested in IVF with GnRHα

Similar oocyte and embryo quality
Dual role of hCG trigger

- Final oocyte maturation
- Early luteal phase stimulation resulting in almost normal Luteal function
- Same dose for both functions?
hCG versus GnRH agonist

Duration of LH surge

LH mean mid-luteal phase
- 6.0 IU/l in natural cycle
- 1.5 IU/l in GnRH a group
- 0.2 IU/l in hCG group

(Tavaniotou and Devroey, 2003) (Humaidan et al, 2005)
hCG versus GnRH agonist

**Serum E₂**

- HCG vs GnRHa
  - P < 0.01

**Serum P**

- HCG vs GnRHa
  - P < 0.01

**VEGF mRNA expression**

- GnRHa: 7
- hCG: 8
  - P < 0.05

**AFT-2 mRNA expression**

- GnRHa: 11
- hCG: 12
  - P = NS
Strategies after GnRH agonist Trigger

- Bolus hCG OPU day
- Luteal Rec LH
- Intense P4 and E2 luteal support
- Freeze all embryos
- Combination

Humaidan et al 2010
Castillo et al 2010
Papanikolau et al 2010
Engman et al 2008
Personalized luteal phase support

Normo-responder patient (< 14 follicles)

Repeat bolus of hCG (1500 IU, OPU + OPU+5) + E2/P4 (Micronized vaginal progesterone 90 mg/day + Oestradiol 4 mg/day) until 7 weeks

OHSS risk patient

- One bolus of hCG (1500 IU, OPU) + E2/P4 (Micronized vaginal progesterone 90 mg/day + Oestradiol 4 mg/day) until week 7
- Rec LH for 10 days from day of OPU
  - 5000 – 30000IU
  - 10000 IU adequate but ideal dose needs to be evaluated
- Total freeze
Hormonal Profile - hCG+P4+E2 vs P4+E2

- **E2**
  - Low dose hCG
  - Serum estradiol:
    - Day 4: *
    - Day 7: *
    - Day 10:
- **P4**
  - Low dose hCG
  - Serum progesterone:
    - Day 4:
    - Day 7:
    - Day 10:
- **LH**
  - E2 + P
  - Low dose hCG
  - Serum LH:
    - Day 4:
    - Day 7:
    - Day 10:
- **Serum VEGF**
  - E2 + P
  - Low dose hCG
  - p = n.s
Ovarian volume

Low dose hCG

E2 + P

Free fluid (cm²)

Garcia-Velasco et al. Fertil Steril 2010
<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial type</th>
<th>Oocyte source</th>
<th>Ovulation trigger</th>
<th>n</th>
<th>OHSS % (n)</th>
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<td>GnRH ± hCG</td>
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<td>own</td>
<td>GnRH ± hCG - cancelled</td>
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<td>Retrospective</td>
<td>donors</td>
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<td>Galindo et al 2009</td>
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<td>GnRH ± hCG</td>
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</table>
Coasting

Cycle cancellation before hCG administration

Specific measures in individual cases

Follicular aspiration

IVM

Cabergoline

Embryo cryopreservation

LOD

Metformin

In PCOS

Intravenous albumin

hydroxyethyl starch
Cryopreservation of all embryos

Continuation of GnRH agonist or antagonist reduces risk of OHSS by preventing endogenous LH surge

Eliminates risk of late OHSS, but early OHSS can still occur if hCG given for trigger

Consider if patient symptomatic at the time of ET - blastocyst culture provides more time to evaluate

Patients may prefer this to cycle cancellation

Endo et al 2002; Lainas et al 2007 RBM Online
Coasting reduces risk to 1.3 - 2.5%.

Widely used - when GnRH agonist protocols were used - 60%

Delvigne et al 2001 Hum Reprod

FSH deprivation may allow smaller follicles to undergo apoptosis

Indirect evidence suggests lower VEGF follicular fluid levels after coasting

No RCTs

Criteria for starting and stopping coasting are not uniform

lower PRs with prolonged coasting
Cabergoline reduces the effects of VEGF-mediated vascular permeability without compromising IR and PR. 

Juan Garcia-Velasco

Molecular mechanism of DA on Vascular Permeability

Gomez et al, Endocrinology 2006; 147:5400-11
Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis

Mohamed A.F.M. Youssef¹,²,*, Madelon van Wely², Mohamed Ahmed Hassan¹, Hesham Gaber Al-Inany¹, Monique Mochtar², Sherif Khattab¹, and Fulco van der Veen²

Significantly lower OHSS incidence in high-risk patients, without compromising pregnancy outcomes
Prophylactic albumin administration at OR

Clear benefit from IV albumin at OR in preventing occurrence of severe OHSS in high risk cases (OR 0.28, 95% CI 0.11 to 0.73)

Hydroxyethyl-starch: (HAES)

- Significantly increases intravascular volume, therefore raising osmotic pressure
- Serum half-life of 10 h
- No anaphylaxis or risk of transfer of infections
- Inhibits platelet aggregation

Beneficial effect in decreasing OHSS

Immunoglobulin:

- Severe OHSS low IgG, IgA gamma globulins
- IV gamma globulins reduce the severity

Adjuvant Therapies

Corticosteroids:

- 100 mg IV hydrocortisone after OR and followed orally
- Prospective RCT did not reduce the OHSS rate Tan et al., 1992
- Administration of methylprednisolone 16 mg per day, starting on day 6 of and tapered by day 13 after ET was effective in significantly reducing OHSS rate (10%) as compared with 43.9% in control group Laines et al., 2003

Graf et al., 1997, König et al., 1998, Gokmen et al., 2001
Prospective RCT showed significant reduction in the incidence of OHSS with LOD

Rimington MR, Walker SM, Shaw RW; Egbase PE, Fukaya et al., 1995; Herve Fernandiz, 2011

LOD did not demonstrate significant differences in LBR and ongoing pregnancy rate, miscarriage or OHSS rates

Adjuvant Therapies

Metformin

Risk of OHSS was significantly decreased in women with PCOS undergoing IVF or ICSI cycles, with a trend for decreased serum E2 levels

Aspirin

Reduced incidence of severe or critical OHSS in GnRH agonist long protocol 100 mg/d aspirin from day 1 of cycle (2/780 vs 43/412, p<.001)

**Follicular aspiration**
**Effect Controversial**
Reduces the incidence and severity
_Coskun S, Whelan JG 3rd, Egbase P E et al Laufer et al., 1990_
Do not prevent OHSS
_Aboulghar et al., 1992; Egbase et al., 1998_

**In - Vitro Maturation of Oocytes**
in PCOS patients, OHSS could be prevented by minimal stimulation and IVM _Child et al., 2001_
Not achieved PRs comparable to conventional IVF _Chan et al., 2003_

**Luteal phase support**
Avoid hCG, Use P4
_Evidence level 1a_
_Ludwig M, Diedrich K_

**Other Therapies**
## Interventions that do not reduce the risk of OHSS

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Grade of evidence</th>
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</thead>
<tbody>
<tr>
<td>Intravenous Albumin</td>
<td>A</td>
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<tr>
<td>Follicle aspiration prior to hCG</td>
<td>A</td>
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<tr>
<td>Rec LH instead of hCG</td>
<td>A</td>
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<tr>
<td>Rec hCG instead of urinary hCG</td>
<td>A</td>
</tr>
<tr>
<td>One type of FSH versus another</td>
<td>A</td>
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</tbody>
</table>
Individualization of Protocols to reduce OHSS

**Follicular Phase**
- AMH
- AFC
- Age
- History

**Day of oocyte trigger**
- Normal Response
- Rec hCG 250 mcg
- GnRHa Triggering 1mg SC

**Luteal Phase**
- sET or DET
- Freeze surplus
- Proven LPS

**Signs of OHSS**
- Freeze all embryos
- Proceed to Day 5
- Evaluate patient
- P4 + E2 + 1500 hCG on day of OR for LPS
- Freeze all embryos
- Freeze half D 2/3 Culture rest to blastocyst
- Freeze surplus

This tailored approach could reduce the incidence of OHSS in women predicted to have excessive response
In the past apart from cancellation, none of the approaches were totally efficient, although they decrease the incidence in patients at high risk of OHSS.

HCG is primary stimulus for the syndrome. Withholding hCG is the main preventive measure. Cycle with cryopreservation all embryos to be transferred in subsequent cycles.
Take home message

GnRH antagonist protocol coupled with GnRHa triggering

Efficient

Safe

Simple

Best method of preventing OHSS in oocyte donors also
However, GnRH agonist trigger leads to lower luteal phase steroidal concentrations.

Take home message:
- LP and early pregnancy support with adequate E2 and P4 supplementation is essential for optimal outcome.
- Single blastocyst transfer is strongly recommended.
- LPS with low doses of hCG in high risk patients, secure a normal pregnancy outcome.
- Significantly higher rate of early pregnancy loss in the GnRHa group.
The Ultimate Goal of ART:

A Single
Healthy
And
Happy Baby

Thank You!!!
Thank You

Dr. Madhuri Patil