What is OHSS?

'Loss of control' over COH

OHSS

Iatrogenic Systemic disease mediated by products released from hyperstimulated ovaries
**Pathophysiology**

- Increased vascular permeability
- Arteriolar vasodilatation
- Ovarian enlargement

**Main clinical features**

- Ascites and effusions
- Intravascular dehydration

**Sequelae**

- Thrombo-embolism
- Renal dysfunction
- ARDS

**Evolution of symptoms**

OHSS develops after HCG administration
- Early, within 9 days of OR
- Late, associated with pregnancy

**Early symptoms**
- Abdominal distension
- Discomfor
- Reduced urine output

**Worsening symptoms**
- Increased pain
- Dyspnoea
- Reduced urine output

**Clinical issues**

- Oliguria in 30%
- Hypoalbuminaemia, hyponatraemia, acidosis
- 29% 
  - Usually mild AST elevation
- Dyspnoea
  - Pleural effusion
  - ARDS

**Mortality**
- ARDS (3 cases)
- Central infection (1 case)
- Renal failure
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

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

Incidence and risk factors

- Moderate or severe OHSS occurs in 3 to 8% of ‘conventional’ IVF cycles
- Incidence in ‘modified’ and ‘mild’ stimulation protocols is unknown, but likely to be lower
- Increased risk if
  - PCO (larger cohort of FSH-sensitive follicles)
  - Increased hCG exposure (multiple preg, hCG luteal support)
  - Previous OHSS
  - ‘Excessive’ ovarian response

All women undergoing ovarian stimulation should be considered potentially at risk of OHSS

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, occasionally hydrothorax.
- Haemoconcentration (Hct >45%, WBC >15,000/ml)
- Oliguria
- Liver dysfunction
- Ovaries usually >12 cm*

Complications
- Renal failure
- Thromboembolism
- ARDS

(Mathur et al 2005, modified from Navot et al 1989)
Prediction of OHSS

- Pre-treatment characteristics
  - PCO
  - Increased antral follicle count
  - Young age
  - Previous OHSS

- Ovarian response parameters
  - Serum variables
    - Follicle numbers
    - FSH/doppler flow indices
  - Egg numbers
  - No agreement on cut-off levels, but widely used in practice
  - Poorly predictive, especially for late OHSS
  - At least 1 in 3 severe OHSS are missed by commonly used criteria of ovarian response

Delvigne et al 1997 Int J Fertil Womens Med 42; 268-70

Serum VEGF as a predictor of OHSS?

- Likely pathogenic agent, levels higher in OHSS cycles
- Is this a marker of ovarian response rather than OHSS per se?

Serum VEGF on its own is poorly predictive of OHSS if ovarian response is taken into account.

Soluble VEGF receptor-1 levels deserve further study.

Basal Serum AMH as a predictor of OHSS

Prospective study of 152 agonist cycles: AMH measured day 3 preceding cycle

OHSS 8%

- AMH cut-off 3.36 ng/ml (DSL ELISA) = highest quartile
- Sensitivity 90.5%
- Specificity 81.3%

Comparison of predictive values for OHSS. ROC AUC of basal serum AMH level was larger than that of age (P = 0.002) and BMI (P < 0.001).

Lee et al 2009 Hum Reprod 23; 140-8
OHSS pathogenesis - clues to prevention?

- HCG
- LH
- Macrophages and granulosa cells
  - IL-2
  - VEGF
  - TNF
  - IL-6, IL-1 etc.
  - Microthrombi
  - Inc. vascular permeability
  - Secondary mediators
  - OHSS

Prevention of OHSS

- Identify high-risk patient and cycle
- Use lower risk treatment
- Specific measures in individual cases

GnRH antagonist vs agonist

- Lower oocyte numbers and oestradiol concentrations may be surrogate markers of a lower risk of OHSS
- Cochrane Meta-analysis (Al-Inany et al 2006) shows a reduced incidence of OHSS and interventions for OHSS with antagonist vs agonist
- Potential for using GnRH agonist triggering of ovulation - lower OHSS risk than hCG trigger


**GnRH antagonist and OHSS**

- Reduced risk, not abolition
- Large observational study found OHSS incidence of 2.1% (53/2524 cycles)
  
- This is very similar to the incidence observed in large studies of GnRH agonist cycles, eg 3.3% (78/2332 cycles)
  

**Coasting**

- Widely used – 60% of 573 ESHRE members surveyed
  
  Delvigne et al 2001 Hum Reprod 16; 2491-5
- FSH deprivation may allow smaller follicles to undergo apoptosis
- Indirect evidence suggests lower VEGF follicular fluid levels after coasting
- No randomised trials, but several observational studies show a lower risk of OHSS in coasted cycles (overall around 2.5%)

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- Criteria for starting and stopping coasting are not uniform. Overall risk of OHSS should be considered. Criteria include E2 levels varying from 2500 – 6000 pg/ml and follicles ≥15mm. Keep in mind lower E2 levels with GnRH antagonist
- Mansour et al 2005 reported 1223 overstimulated cycles with coasting. OHSS occurred in 16 cases (1.3%). No OHSS when E2 <11000 pmol/l on day of HCG
- When to stop coasting -
  - E2 declines to “safe” levels, usually around 3000 pg/ml (11000 pmol/l)
  - If response has not settled in 3-4 days of coasting, as there may be a lower pregnancy rate with prolonged coasting. However, pregnancies can still occur despite prolonged coasting
Coasting + GnRH ant for over-response

- Over-response in GnRH agonist cycles managed by reducing FSH dose, stopping agonist and introducing ganirelix 250 mcg sc daily
- Significant E2 drop on starting antagonist

Cryopreservation of all embryos

- Eliminates risk of late OHSS, but early OHSS can still occur
- Patients may prefer this to cycle cancellation
- Consider especially if patient is symptomatic at the time of embryo transfer – blastocyst culture may provide more time to evaluate
- Continuation of GnRH agonist (or antagonist) reduces risk of OHSS by preventing endogenous LH surge

Dopamine Agonists

- VEGF activation in OHSS appears to be associated with reduced Dopamine activity, from gene array studies
- In the rat OHSS model, low dose Dopamine agonist inhibited VEGF-induced vascular permeability rise, without affecting angiogenesis
- RCT in oocyte donors with >20 oocytes showed reduced incidence of moderate but not severe OHSS in group treated with Cabergoline 0.5 mg daily from OR for 8 days
- Cabergoline treated group had lower incidence of ascites and lower vascular permeability assessed by dynamic contrast-enhanced MRI

Gustafson et al 2006 Hum Reprod 21; 2830-7
Endo et al 2002; Lainas et al 2007 RBM Online
Gomez et al 2006 Endocrinology 2400-11
Dopamine Agonists

- RCT of Quinagolide showed reduced incidence of moderate/severe early OHSS with Quinagolide started 2 hours before HCG and continued until pregnancy test. Significant effect only with 200 mcg daily, with significant side effects.
- However, magnitude of benefit and whether Dopamine Agonists prevent late OHSS remains unclear.
  - Carizza et al. RBM Online 17, 6. 2008 751-755

Metformin co-treatment in women with PCOS

- Insulin stimulates VEGF expression and secretion
- Placebo-controlled RCT of women with PCOS undergoing IVF found lower incidence of OHSS in group receiving 850 mg metformin bd from day of down-reg to OR (Tang et al 2005)
- Systematic review of 5 RCTs showed benefit from metformin co-treatment (12/216 vs 44/210, OR 0.21 CI 0.11-0.410 (Costello et al 2005)

Aspirin for OHSS prophylaxis?

- Rationale: prevent platelet activation and release of inflammatory mediators
- Reduced incidence of severe or critical OHSS in long protocol agonist treated patients receiving 100 mg/d aspirin from day 1 of cycle (2/780 vs 43/412 p<.001)
- However, randomisation validity and OHSS ascertainment unclear
### Interventions that do not reduce the risk of OHSS

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Grade of Evidence</th>
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<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>Recombinant LH instead of HCG</td>
<td>A</td>
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<tr>
<td>Rec HCG instead of urinary HCG</td>
<td>A</td>
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<tr>
<td>One type of FSH versus another</td>
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#### Components of OHSS
- Macrophages and granulosa cells
- Aspirin
- Cabergoline
- Dopamine
- Angiotensin antagonists

#### Secondary mediators
- Microthrombi
- Increased vascular permeability

#### Management Strategies
- Cancellation, cryopreservation
- Continue GnRHa after cancellation
- Coasting
- Metformin
- Cabergoline
- Dopamine
- Aspirin
- Angiotensin antagonists

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**THE MANAGEMENT OF OVARIAN HYPERSTIMULATION SYNDROME**

Many staff who assess and manage women with OHSS will be unfamiliar with the condition, hence minimal consensus treatment frequently takes place outside the hospital setting, and serious OHSS is uncommon. Both education and communication is particularly important in providing safe and effective care to women with OHSS. Units caring for patients that have a potential for resulting in OHSS should develop agreed protocols for referral of women with suspected OHSS to hospital care, including written protocols for initial OHSS management. Protocols should be available to referring practitioners, neighboring gynaecology departments and accident and emergency departments in their catchment area.
OHSS – patient awareness and information

- Early signs
- Worsening signs
- Need to seek medical help
- 24 hour contact
- Mention ovarian stimulation if seeking ANY medical assistance

Out-patient management

Patient selection
- Mild/mod OHSS
- Able to attend for follow-up

Counselling
- Fluid intake
- Analgesia

Monitoring
- Daily phone call
- At baseline and every 2 to 3 days till recovery
- CBC, U&Es, LFT, weight, abdominal girth

Indications for admission
- Any sign of severe OHSS
- Unable to control pain/nausea
- Unable to eat/drink
- Shortness of breath
- Oliguria

Daily Monitoring
- Weight
- Abdominal girth
- Intake and output
- FBC, haematocrit
- Urea and Electrolytes
- Liver Function Tests

Plus
- Routine observations
- Chest X Ray
- ECG
- Abdominal/pelvic US
- Thrombophilia screen

Hospital admission

Indications for admission
- Severe pain
- Unable to eat or drink
- Oliguria
- Shortness of breath
- Any sign of Severe OHSS
Inpatient care

- **Pain Relief**
  - Paracetamol/codeine
  - No NSAID
  - Consider another cause of pain e.g., ectopic, ovarian torsion

- **Fluid Management**
  - Allow to drink to thirst
  - IV fluids only for initial rehydration or if unable to drink normally
  - Use albumin if saline fails to correct dehydration

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Inpatient care

- **Drainage of ascites and effusions**
  - **Indications**
    - Severe distension causing distress or difficulty breathing
    - Poor urine output despite rehydration
    - Prolonged course
    - Under ultrasound guidance
    - Indwelling catheter
    - Replace albumin

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Inpatient care

- **Prevention of thrombosis**
  - Can occur after apparent improvement
  - Commonly affects upper body
  - Reported up to 20 weeks of pregnancy
  - May occur despite prophylactic heparin
  - RCOG guidelines advise low molecular weight heparin (e.g., Clexane) for all in-patients, especially if dehydration or reduced mobility
  - If pregnant, continue at least till the end of first trimester
Case Study

- 37 year old, IVF for unexplained infertility
- 24 eggs, severe OHSS. Admitted, paracentesis x 4
- Discharged after 4 weeks, ongoing twin pregnancy, moved to Cambridge
- Abdominal pain - normal scan, settled
- Started low mol wt heparin
- Weekly review - well, minor neck discomfort
Future directions

- Better dissemination of existing evidence base
- “Mild” stimulation for IVF
- Single embryo transfer
- In vitro maturation of oocytes
- RCT of dopamine agonist versus coasting
- Future selective VEGF antagonists
- Trial of early paracentesis vs conservative approach