PREVENTION AND MANAGEMENT OF OVARIAN HYPERSTIMULATION SYNDROME

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Conflict of interest

None

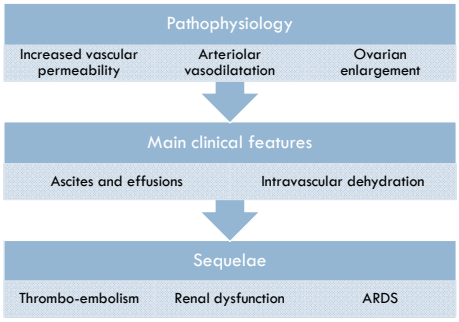
What is OHSS?

'Loss of control' over COH

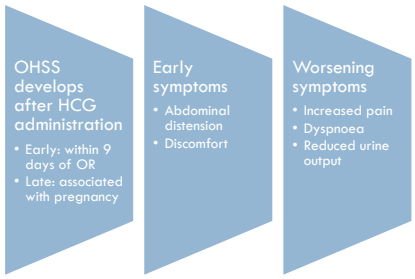
↓

OHSS

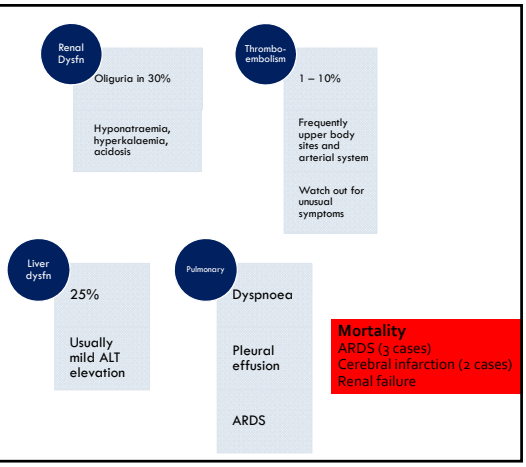
Iatrogenic **Systemic disease mediated by products released from hyperstimulated ovaries**



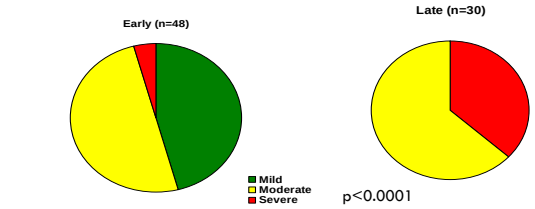
Evolution of symptoms



Clinical issues



Late OHSS is more likely to be severe than early OHSS



p<0.0001

Early OHSS ≤ 9 days of oocyte retrieval
Late OHSS > 9 days after OR

Late OHSS is more difficult to predict from ovarian response

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*

Complications
Renal failure
Thromboembolism
ARDS

Severe
Clinical ascites, occasionally 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)

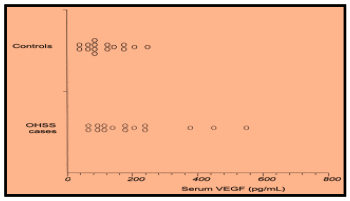
Prediction of OHSS

- Pre-treatment characteristics
  - PCO
  - Increased antral follicle count
  - Young age
  - Previous OHSS
- Ovarian response parameters
  - Serum oestradiol
  - Follicle numbers
  - Power 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?



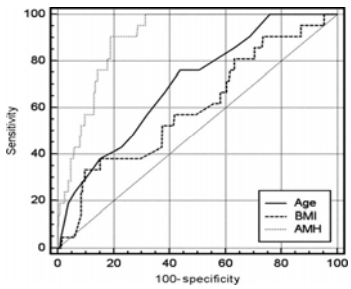
Serum VEGF on its own is poorly predictive of OHSS if ovarian response is taken into account

Mathur et al Fertil Steril. 2002 78:154-8

Soluble VEGF receptor-1 levels deserve further study

Pau et al Hum Reprod. 2006 21:1453-60

Basal Serum AMH as a predictor of OHSS



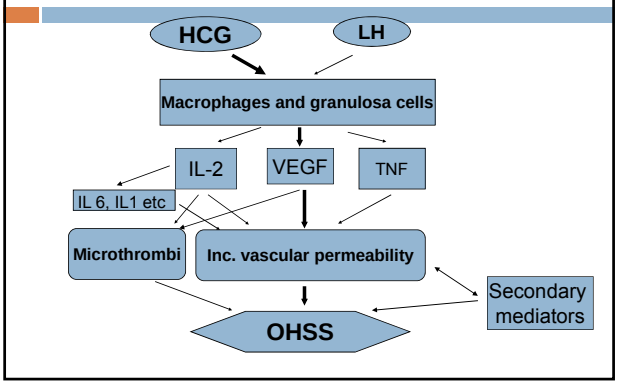
Prospective study of 262 agonist cycles: AMH measured day 3 preceding cycle
OHSS 8%

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

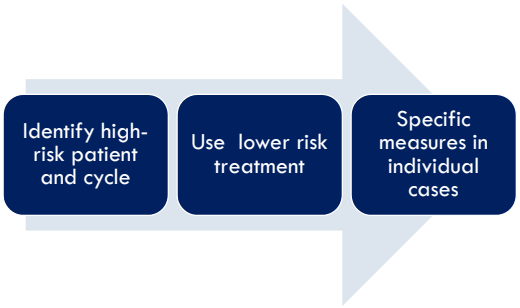
Comparison of predictive values for OHSS. ROC AUC of basal serum AMH level was larger than that of age (P = 0.002) and BMI (P < 0.001).

Lee et al (2008)Hum Reprod 23; 160-8

OHSS pathogenesis - clues to prevention?



Prevention of OHSS



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)

Papanikolau et al (2006) Fertil Steril 85; 112-20

- This is very similar to the incidence observed in large studies of GnRH agonist cycles, eg 3.3% (78/2332 cycles)

Mathur et al (2000) Fertil Steril73; 901-7

Coasting

- Widely used – 60% of 573 ESHRE members surveyed

Delvigne et al 2001 Hum Reprod 16; 2491-5

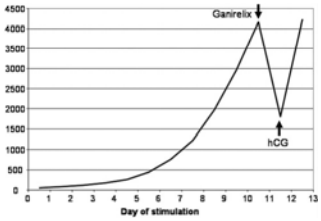
- FSH deprivation may allow smaller follicles to undergo apoptosis
- Indirect evidence suggests lower VEGF follicular fluid levels after coasting
- No randomised trials, but several observational studies show a lower risk of OHSS in coasted cycles (overall around 2.5%)

Coasting

- 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



Retrospective report of 87 agonist cycles with over-response
Sev OHSS 2/87 (2.3%)

Gustofson et al 2006 Hum Reprod 21; 2830-7

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

Endo et al 2002; Lainas et al 2007 RBM Online

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**

Gomez et al 2006 Endocrinology 2400-11

- 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 MR

Alvarez et al (2007) J Clin Endocrinol Metab 92(8):2931-7

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

  Busso et al Hum Reprod, 25; 4, 995–1004, 2010

- 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)

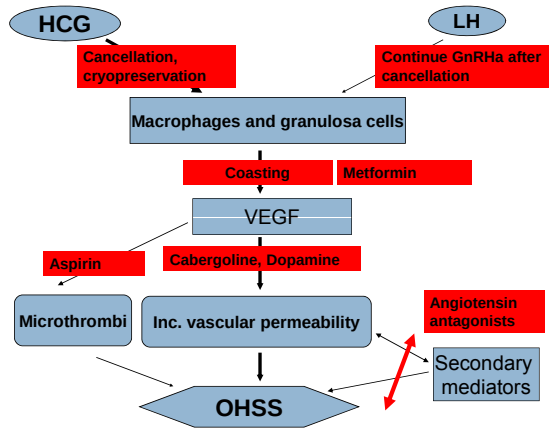
Aspirin for OHSS prophylaxis?

- 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

Varnagy et al (2009) Fertil Steril doi:10.1016/j.fertnstert.2009.01.085

Interventions that do not reduce the risk of OHSS

Intervention	Grade of Evidence
Intravenous Albumin	A
Follicle Aspiration prior to HCG	A
Recombinant LH instead of HCG	A
Rec HCG instead of urinary HCG	A
One type of FSH versus another	A



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Green-top Guideline No. 5

THE MANAGEMENT OF OVARIAN HYPERSTIMULATION SYNDROME

Many staff who assess and manage women with OHSS will be unfamiliar with the condition, because assisted conception treatment frequently takes place outside the hospital setting and serious OHSS is uncommon. Thus, education and communication is particularly important in providing safe and effective care to women with OHSS.

Units carrying out treatment that has 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, neighbouring gynaecology departments and accident and emergency departments in their catchment areas. C

OHSS – patient awareness and information

Ovarian hyperstimulation syndrome – what you need to know

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

Out-patient management

Hospital admission

Indications for admission

- Severe pain
- Unable to eat or drink
- Oliguria
- Shortness of breath
- Any sign of Severe OHSS

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

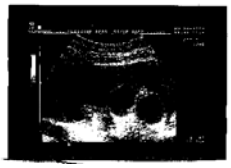
As reqd.

Inpatient care

- Pain Relief
  - Paracetamol/codeine
  - No NSAID
  - Consider another cause of pain eg, 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

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



Inpatient care

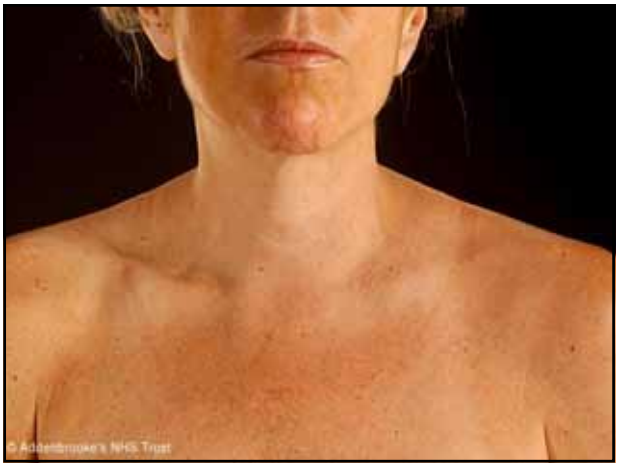
- Prevention of thrombosis
  - Can occur after apparent improvement
  - Commonly affects upper body
  - Reported upto 20 weeks of pregnancy
  - May occur despite prophylactic heparin
  - RCOG guidelines advise low molecular weight heparin (eg Clexane) for all in-patients, especially if dehydration or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

9.2 Who should provide care to women with OHSS?

Multidisciplinary assistance should be sought for all women with critical or severe OHSS who have persistent haemoconcentration and dehydration.	✓
Features of critical OHSS should prompt consideration of the need for intensive care.	C
A doctor experienced in managing OHSS should remain in overall charge to provide information concerning OHSS to other personnel, who may not have experience of managing this condition.	✓
Pelvic surgery should be restricted to cases with adnexal torsion or co-incident problems requiring surgery and only undertaken by an experienced surgeon following careful assessment.	C

Case Study

- *37 year old, IVF for unexplained infertility*
- *24 eggs, sev 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