How do we assess OHSS by ultrasound. - what are the high risk markers

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Outline of the presentation

• Ovarian hyperstimulation syndrome (OHSS)
• Risk Factors for OHSS
• Prediction I Before stimulation
• Prediction II During ovarian stimulation
• Summary
Ovarian hyperstimulation syndrome (OHSS)

- Ovarian hyperstimulation syndrome (OHSS) is an uncommon but serious complication associated with controlled ovarian stimulation during assisted reproductive technology (ART).

- Moderate-to-severe OHSS occurs in approximately 1%-5% of cycles.

- OHSS is characterized by cystic enlargement of the ovaries and transudation of fluid and proteins from the intravascular compartment into the third space due to increased capillary permeability.

Fertil Steril 2016;106:1634-47
Risk Factors for OHSS

Primary Risk Factors

• Young age
• Low body weight
• PCOS, or isolated PCOS characteristics because of increased number of recruitable follicles
• H/O previous OHSS or increased response to gonadotropin therapy.

Secondary Risk Factors

• Factors which become apparent during stimulation include:
  • Absolute levels of E2 > 3,000 pg/ml or rate of increase of serum E2
  • Follicular size and number (>20) on both ovaries
  • Number of oocytes collected.

international Journal of Infertility and Fetal Medicine, Vol. 4, No. 3
Need for Prediction of OHSS

• Develop ovarian stimulation routines that are associated with a per se decreased risk of OHSS

• Also need measures of OHSS prevention for individual patients, which are safe and efficacious, and can therefore be liberally utilized
Prediction of OHSS

• **Prediction I**  Before stimulation

• **Prediction II**  During ovarian stimulation
Antral follicle count (AFC)

- AFC is the sum of antral follicles in both ovaries, as observed with transvaginal ultrasonography during the early follicular phase. Antral follicles defined as measuring 2–10mm in mean diameter in the greatest two-dimensional plane.
Prediction of OHSS at different antral follicle count thresholds in a prospective cohort of 1,012 women

A total of 1,012 consecutive subjects of all ages undergoing their first cycle of assisted reproductive technique

- The risk of moderate or severe OHSS is 2.2% with AFC of < 24, the risk increases to 8.6% at AFC of > 24.
- The risk of OHSS increases further to 11% if there are signs and symptoms of polycystic ovary syndrome. CoFertil Steril 2012;98:657–63.
Prediction of OHSS at different antral follicle count thresholds in a prospective cohort of 1,012 women

- The risk of OHSS increased in a linear fashion from 8.4% to approximately 21% as the AFC threshold increased from 24 or more.
- The risk of OHSS continued to rise in a linear fashion to an AFC of 41 or more but then plateaued.

Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization

- AFC performs well as a test for ovarian response being superior or at least similar to complex expensive and time consuming endocrine tests.

- Total volume of the ovaries detected by transvaginal ultrasound is correlated with the outcome parameters but not better than the count of antral follicles. Its performance was slightly to moderately less than that of AFC, both for poor and high response.

Reproductive Biology and Endocrinology 2007, 5:9
Optimal follicle and oocyte numbers for cryopreservation of all embryos in IVF cycles at risk of OHSS

Positive predictive value using numbers of follicles or oocytes to predict early-onset ovarian hyperstimulation syndrome among women with 20 or more oocytes retrieved.

A retrospective study of 2253 cycles identified a threshold of 24 or more retrieved oocytes to recommend a freeze-all cycle, a strategy in which a fresh transfer is avoided to allow the ovaries to return to a normal state before attempting pregnancy in order to prevent OHSS.

RBMOnline - Vol 17. No 3. 2008 312-317
Can quantitative three-dimensional power Doppler angiography be used to predict ovarian hyperstimulation syndrome?

- 118 subjects undergoing IVF had a three-dimensional (3D) TVS in early follicular phase of menstrual cycle preceding IVF treatment.
- 18 of them developed moderate or severe OHSS and 100 subjects had normal ovarian response.
- AFC, ovarian volume, and ovarian vascularity (vascularization index (VI), flow index (FI) and vascularization flow index (VFI)) were compared between OHSS and control groups.
- The study demonstrated that women developing OHSS during IVF do not demonstrate an increased ovarian blood flow as measured by 3D ultrasound but do have a significantly higher antral follicle count, which is the only significant predictor of OHSS.

*Ultrasound Obstet Gynecol.* 2009 May;33(5):583-91
Doppler in PCOS to predict OHSS

- The use of Doppler to assess ovarian stromal flow in women with PCO may have a useful predictive role for the future development of OHSS.

- Patients with PCO who have a high ovarian stromal flow are more likely to be at risk of ovarian hyperstimulation during treatment.
Prediction of OHSS During stimulation
The number of follicles on the day of HCG administration - indicator for the occurrence of severe OHSS

The number of follicles on the day of HCG administration appears to be a better prognostic indicator for the occurrence of severe OHSS than the estradiol values (87% of the severe cases had \( \geq 14 \) or follicles of a diameter \( \geq 11 \text{mm} \), whereas only 50% of them had an estradiol value 3000 ng/l).
Ovarian hyperstimulation syndrome: prediction by number and size of preovulatory ovarian follicles

- 65 infertile patients treated with hMG for ovulation induction and human chorionic gonadotropin (hCG). 5A specific preovulatory follicular configuration characterizes mild and severe hyperstimulation.

- Mild OHS was characterized by the presence of eight to nine follicles, 68.7% of which were of intermediate size (9 to 15 mm).

- In moderate to severe OHS 95% of the preovulatory follicles were < 16 mm, most of them (54.7%) < 9 mm in diameter.

- It can be concluded that this is important information before hCG administration and emphasizes the value of ovarian ultrasonography in predicting OHS.
Number of follicles VS E2 concentrations for the purpose of prediction of OHSS

- Predictive value of the optimal threshold of >13 follicles (85.5% sensitivity; 69% specificity) was statistically significantly superior to the optimal threshold of 2,560 ng/L for E2 concentrations (53% sensitivity, 77% specificity) in identifying patients at risk for OHSS.

- A threshold of >18 follicles and/or E2 of >5,000 ng/L yields an 83% sensitivity rate with a specificity as high as 84% for the severe OHSS cases.

1,801 patients who underwent 2,524 cycles.

Analysis for several E2 concentrations and number of follicles with a diameter of >11 mm.
The number of follicles can discriminate the patients who are at risk for developing OHSS, whereas E2 concentrations are less reliable for the purpose of prediction.
Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles

SART data from 2008-2010, the incidence of OHSS was 0.37% in fresh cycles with six to 10 oocytes and 1.67% in fresh cycles with 16-20 oocytes.

Rates of live birth and ovarian hyperstimulation syndrome with increasing oocyte yield Based on Society for Assisted Reproductive Technology (SART) data from 2008-2010.
The risk for ovarian hyperstimulation syndrome significantly increases and live birth rates plateau in patients with >15 oocytes retrieved: an analysis of 256,381 fresh, autologous IVF cycles.

Retrieval of >15 oocytes significantly increases the risk of OHSS with minimal gain in LB rate.

Fertil. Steril. 101, 967–
ROC for retrieved oocyte number as a predictor of ovarian hyperstimulation syndrome.

Oocyte number thresholds: A: 5; B: 10; C: 15; D: 20; E: 25.

OHSS prediction before hCG administration

624 ICSI patients. Observational clinical data were compared. Patients who developed OHSS were compared with patients who did not develop OHSS. Twenty-eight patients developed OHSS considered as severe.

The only independent predictor of OHSS before the ovulatory dose of hCG was total number of medium/large-sized follicles before hCG. A corresponding ROC found a sensitivity of 82.1% and specificity of 79.4%.

OHSS prediction after oocyte aspiration

After oocyte aspiration, the variables number of follicles at oocyte aspiration, number of aspirated oocytes and total number of medium/large-sized follicles before hCG were predictive of OHSS. Women with a high risk of OHSS requiring hospitalization could be identified with reasonable high sensitivity and specificity by a combination of these predictors.

624 ICSI patients. Observational clinical data were compared. Patients who developed OHSS were compared with patients who did not develop OHSS. Twenty-eight patients developed OHSS considered as severe.
### Classification of OHSS symptoms

<table>
<thead>
<tr>
<th>OHSS stage</th>
<th>Clinical feature</th>
<th>Laboratory feature</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Abdominal distension/discomfort</td>
<td>No important alterations</td>
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<tr>
<td></td>
<td>Mild nausea/vomiting</td>
<td>Protocol alterations</td>
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<tr>
<td></td>
<td>Mild dyspnea</td>
<td>Protocol alterations</td>
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<td></td>
<td>Diarrhea</td>
<td>Protocol alterations</td>
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<tr>
<td></td>
<td>Enlarged ovaries</td>
<td>Protocol alterations</td>
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<tr>
<td>Moderate</td>
<td>Mild features</td>
<td>Hemoconcentration (Hct &gt;41%)</td>
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<td></td>
<td>Ultrasonographic evidence of ascites</td>
<td>Elevated WBC (&gt;15,000 mL)</td>
</tr>
<tr>
<td>Severe</td>
<td>Mild and moderate features</td>
<td>Severe hemoconcentration (Hct &gt;55%)</td>
</tr>
<tr>
<td></td>
<td>Clinical evidence of ascites</td>
<td>WBC &gt; 25,000 mL</td>
</tr>
<tr>
<td></td>
<td>Hydrothorax</td>
<td>CrCl &lt;50 mL/min</td>
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<tr>
<td></td>
<td>Severe dyspnea</td>
<td>Cr &gt;1.6 mg/dL</td>
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<tr>
<td></td>
<td>Oliguria/anuria</td>
<td>Na+ &lt;135 mEq/L</td>
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<td></td>
<td>Intractable nausea/vomiting</td>
<td>K+ &gt;5 mEq/L</td>
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<td></td>
<td>Low blood/central venous pressure</td>
<td>Elevated liver enzymes</td>
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<tr>
<td></td>
<td>Pleural effusion</td>
<td>Protocol alterations</td>
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<td></td>
<td>Rapid weight gain (&gt;1 kg in 24 h)</td>
<td>Protocol alterations</td>
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<tr>
<td></td>
<td>Syncope</td>
<td>Protocol alterations</td>
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<tr>
<td></td>
<td>Severe abdominal pain</td>
<td>Protocol alterations</td>
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<tr>
<td></td>
<td>Venous thrombosis</td>
<td>Protocol alterations</td>
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<tr>
<td>Critical</td>
<td>Anuria/acute renal failure</td>
<td>Worsening of findings</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia</td>
<td>Protocol alterations</td>
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<td></td>
<td>Thromboembolism</td>
<td>Protocol alterations</td>
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<tr>
<td></td>
<td>Pericardial effusion</td>
<td>Protocol alterations</td>
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<td></td>
<td>Massive hydrothorax</td>
<td>Protocol alterations</td>
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<tr>
<td></td>
<td>Arterial thrombosis</td>
<td>Protocol alterations</td>
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<td>Adult respiratory distress syndrome</td>
<td>Protocol alterations</td>
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<td></td>
<td>Sepsis</td>
<td>Protocol alterations</td>
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</tbody>
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Note: Hct = hematocrit; WBC = white blood cell; CrCl = creatinine clearance; Cr = creatinine; Na+ = sodium; K+ = potassium.
Ovarian hyperstimulation syndrome.

Multiple large anechoic cysts are visualized in both ovaries in this image.
Ultrasound of moderate OHSS with ascites.
Ultrasound of ascites in the cul-de-sac with severe OHSS
Internal jugular vein thrombosis and ohss

Figure 1 A: Ultrasound image in transverse plane at the level of the thyroid (T). The right internal jugular vein (IJV) is enlarged containing echogenic thrombus. B: Longitudinal ultrasound image showing flow above the level of thrombus (Th) on colour Doppler. Internal jugular vein (IJV). (In colour online)

Figure 2 A: Longitudinal ultrasound image of the left upper quadrant of the abdomen showing moderate pleural effusion (P) and ascites (A) surrounding the spleen (S). B: Longitudinal ultrasound image of the pelvis showing a markedly enlarged right ovary (O).
Severe OHSS

https://radiopaedia.org/cases/ovarian-hyperstimulation-syndrome
For the younger individual, careful assessment and identification of the “high-responder” should guide the clinician in choosing the optimal, gentlest stimulation, thus avoiding or diminishing the risk of OHSS.
The syndrome almost always presents either 3–7 days after hCG administration in susceptible patients (early onset) or during early pregnancy, 12–17 days after hCG administration (late onset).

Early OHSS can to some extent be predicted by pre-ovulatory indices of ovarian response, in time to institute preventive measures such as cancellation (Hancock et al., 1970).

Late OHSS does not relate strongly to pre-ovulatory ovarian response, making it difficult for clinicians to identify the cycles in which it is likely to occur.
Elimination of ovarian hyperstimulation syndrome

- If the combined GnRH antagonist/agonist or the tailored COS protocols yield >20 oocytes, or >10 embryos develop, the patient should be followed for 5 days after oocyte retrieval for signs of early OHSS (ultrasonographic signs of ascites, Hct levels for the degree of haemoconcentration).

- If signs develop, embryo transfer should be withheld and all resulting embryos cryopreserved. This will limit early OHSS, if it appears, to a milder and shorter form.

- If it does not appear, the transfer of one blastocyst will decrease the risk of multiple pregnancy to almost zero, thereby eliminating the risk of late OHSS.

- **Human Reproduction Vol.20, No.2 pp. 320–322, 2005**
While cut points require validation, AMH values >3.4 ng/mL, AFC >24, development of ≥25 follicles, estradiol values >3,500 pg/mL, or ≥24 oocytes retrieved are particularly associated with an increased risk of OHSS
Summary

The number of follicles on the day of HCG administration appears to be a better prognostic indicator for the occurrence of severe OHSS than the estradiol values. AFC >24, development of > 25 follicles, or > 24 oocytes retrieved are particularly associated with an increased risk of OHSS.

For patients with 19 follicles or more > 11 mm on the day of hCG, measures to prevent the development of OHSS should be considered.
If the combined GnRH antagonist/agonist or the tailored COS protocols yield >20 oocytes, or >10 embryos develop, the patient should be followed for 5 days after oocyte retrieval for signs of early OHSS (ultrasonographic signs of ascites, Hct levels for the degree of haemoconcentration).

If signs develop, embryo transfer should be withheld and all resulting embryos cryopreserved. This will limit early OHSS, if it appears, to a milder and shorter form.