

**OVARIAN HYPERSTIMULATION SYNDROME**



*“Hylas and the Nymphs”, John William Waterhouse, oil on canvas, 1896, Manchester City Art Gallery, Manchester*

*Hylas then came to a spring that was known as The Fountains  
by local inhabitants. Just now, as it chanced, the dances  
of the nymphs who dwelt around that lovely mountain,  
ever to honor Artemis with nocturnal song.  
Now all whose haunts were hilltops or mountain torrents,*

*the guardian wood nymphs, these were ranged apart;  
but one water nymph had just swum up to the surface  
of the sweet flowing-spring. Before her she saw young Hylas  
in a blushing glow of sweet gracefulness and beauty:  
for on him the full moon, shining clear from heaven,  
now cast its light. Aphrodite fluttered her senses,  
leaving her stunned, scarce able to gather her wits.  
But the moment he dipped his pitcher in the current,  
crouching over sideways, and the brimful stream rang loud,  
as it hit the echoing bronze, then she at once  
slipped her left arm round his neck from above, in urgent  
longing to kiss his tender young mouth, and with her  
right hand drew down his elbow, plunged him into mid-eddy.*

*The Argonautika, (Jason and the Argonauts)  
3<sup>rd</sup> Century B.C, Bk I, 1221-1239.  
Apollonius of Rhodes (c. 305-235 B.C)*

*In ancient Greek mythology Nymphs were a type of nature goddess, semi-divine creatures who lived in the countryside and were connected with particular aspects of nature, such as rivers, wells, rocks, mountains, forests or trees. Most Nymphs were benevolent and could grant prosperity to humans. They were also worshipped in the hope of the provision of fertility. Nevertheless they had to be treated with caution as they also had a sinister side. Water Nymphs, or Naiads, in particular had the power to seduce mortals, such as Hylas, as depicted in John William Waterhouse's painting, and drive them insane or lure them into wells or rivers where they would drown.*

*In the 21<sup>st</sup> century humans no longer rely on water nymphs for the promotion of fertility. The marvels of modern medicine have provided a range of wondrous drugs to take their place. Like the nymphs, however, these drugs need to be treated with caution as they also have a sinister side in the form of OHSS and its "watery" complications.*

## OVARIAN HYPERSTIMULATION SYNDROME

### Introduction

**Ovarian hyperstimulation syndrome (OHSS)** is an iatrogenic complication of ovulation induction by drug therapy.

It is potentially the most serious complication of controlled ovarian hyperstimulation for assisted reproduction technologies.

It occurs when the ovaries are hyperstimulated and enlarged due to fertility treatments and results in the shift of plasma from the intravascular space to third spaces, predominantly the peritoneal cavity.

In most cases the symptoms are mild tend to be self limiting (**typically lasting 10-14 days**) and will do well with **supportive treatment**, however in a small number of cases it can be severe and even life threatening.

**The syndrome is more prolonged and more severe in women who are pregnant.**

It is more frequently seen in:

- Younger patients, (less than 35 years)
- Patients less than 60 kgms.
- Patients with polycystic ovarian syndrome.

The syndrome is characterized clinically by

1. **Ovarian enlargement.**
2. **Increased vascular permeability.**

The condition tends to be more severe if the patient is pregnant.

### Epidemiology

The incidence of OHSS is approximately low at approximately 5 % following ovulation induction with exogenous gonadotrophins.

The World Health Organization (WHO) has estimated the incidence of severe OHSS to be 0.2 to 1 % of all stimulation cycles.<sup>1</sup>

### Pathophysiology

The pathophysiology of OHSS is not fully understood, but increased capillary permeability with the resulting loss of fluid into third spaces is its main feature.

In the susceptible individuals, gonadotrophins administration for final follicular maturation and triggering of ovulation appears to be the pivotal stimulus for OHSS, leading to:

- Excessive production of vascular endothelial growth factor (VEGF) in the ovary
- Release into the circulation of vasoactive-angiogenic substances that lead to increased vascular permeability, with loss of fluid to third spaces

Risk factors:

It is more frequently seen in:

1. Patients with polycystic ovarian syndrome.
2. Patients with a previous episode of OHSS
3. High (or rapidly rising) serum estradiol concentrations
4. Pregnancy:
  - Which increases not only the risk of **late** OHSS, but also the **duration** and **severity** of OHSS (due to the persistent stimulation by endogenous hCG).

*Less certainly:*

5. Younger patients, (less than 35 years)
6. Patients less than 60 kgms.

Complications

These include:

1. Hypotension:

Due to contracted intravascular space, with transudate fluid losses into third spaces, including:

  - Peritoneal space (most commonly)
  - Pleural space (uncommon)
  - Pericardial space (rarely).
2. Dehydration/ electrolyte disturbances:

- Due to vomiting
- 3. Renal impairment/ failures
- 4. Respiratory distress:
  - ARDS
- 5. Increased risk of ovarian torsion.
- 6. Increased susceptibility to sepsis
- 7. Increased susceptibility to thromboembolic disease.
  - The occurrence of these events is likely to be related to hemoconcentration and to hypercoagulation associated with elevated serum estrogen concentrations.
  - These events may be arterial or venous.

### Classification of the Severity of OHSS

OHSS can be classified as **mild, moderate, severe** and critical as follows:

#### Mild

- Mild abdominal pain
- No clinically apparent ascites.
- No Abdominal ascites detected on ultrasound.
- Ovarian size < 8 cm
- No clinically important laboratory findings.

#### Moderate

- Moderate abdominal pain
- Abdominal ascites detected **ultrasound examination.**
- Nausea and vomiting
- Ovarian size 8 - 12 cm
- Hematocrit > 41 % up to 0.45 and WCC > 15,000

- Estradiol levels, 10,000 - 20,000 pmol/L

### Severe

- Moderate to severe abdominal pain
- Abdominal ascites detected clinically.
- Pleural effusion
- Intractable nausea and vomiting
- Ovarian size >12 cm
- Hematocrit > 0.55 and WCC > 25,000
- Elevated liver enzymes
- Estradiol levels, 20,000 – 30,000 pmol/L
- Oliguria

### Critical

#### **In critical OHSS, the function of vital organs and systems is compromised**

- Moderate to severe abdominal pain
- Abdominal ascites detected clinically.
- Intractable nausea and vomiting
- Ovarian size >12 cm
- Hematocrit as above and worsening.
- Estradiol levels, 20,000 - 30,000 pmol/L or higher

#### *Together with clinical complications:*

- Renal failure
- Pleural and pericardial effusions, causing dyspnea and hypotension.
- Thrombo-embolic events.
- Cardiovascular collapse

- ARDS

### Clinical Features

The OHSS syndrome is essentially characterized clinically by:

1. **Ovarian enlargement.**
2. **Increased vascular permeability.**

The diagnosis of (OHSS) is made by a combination of:

1. **History of ovarian stimulation followed by ovulation or administration of human chorionic gonadotropin (hCG).**
2. **Typical clinical features**
3. **Transvaginal ultrasound findings (enlarged ovaries**

Once the diagnosis of ovarian hyperstimulation syndrome is made, disease severity should be classified as **mild, moderate, severe, or critical** (see above).

### Important points of History:

*Patients will most commonly present with:*

1. Abdominal pain.
2. Abdominal distension.

*Less commonly with:*

3. Shortness of breath.

*If the condition is severe:*

4. Cardiovascular collapse

Note that intravascular fluid loss may be:

- Occult or “third space”
  - Co-existent with peripheral and pulmonary edema.
5. Thrombo-embolic events.

### Important points of Examination:

1. Vital signs:

- Check for signs of sepsis (fever) and/ or circulatory compromise.
- In addition to the usual vital signs; monitoring and measurement of *weight and abdominal circumference* should also be done, (in the ward these will subsequently be re-measured on a daily basis)

2. Abdominal tenderness which is mild and diffuse:

Note that if there is significant local tenderness / guarding / peritonism found on examination, other important differential diagnoses or secondary complications will need to be considered including:

- Ectopic pregnancy
- Ovarian torsion or bleeding.
- Other intra-abdominal sepsis.

3. Asses for signs of third space complications:

- Ascites
- Pleural effusion.
- Cardiac tamponade

4. PV:

- If this is considered necessary, care should be taken (as it should for a vaginal ultrasound) so as not to rupture large ovarian cysts.

### Investigations

These will be guided by the clinical severity of the presentation and not all will be necessary in all cases, but the following will need to be considered:

#### Blood tests:

1. FBE:

- Especially for hematocrit and WCC.

2. CRP

3. U&Es / glucose
4. Beta HCG
5. Clotting profile.
  - Include a thrombophilia screen in patients with thromboembolic events.
6. LFTs
7. Estradiol (E2) levels.

### Ultrasound:

#### **This is the most important investigation.**

- Ovarian size is measured.
- To assist in ruling out alternative diagnoses, (bleed into a cyst or torsion of a cyst, ectopic pregnancy)
- Detect ascites.

### CXR:

- This should be done if there are significant respiratory symptoms or pleural effusion is suspected.
- Appropriate shielding should be provided.

### ECG:

- If the patient is significantly unwell or pericardial effusion is suspected.

### Echocardiography:

- This should be done if pericardial effusion is suspected.

It will confirm the presence of pericardial fluid and detect any evidence of cardiac tamponade.

### Management

Treatment is predominantly supportive and most cases will be mild and self-limiting and can be managed as outpatients.

Mild OHSS can progress to moderate or severe OHSS, particularly if pregnancy has occurred.

Therefore, women with mild disease should be observed closely for worsening abdominal pain, excessive weight gain (>1 kg/day), and increasing abdominal girth

Those with more severe symptoms and/ or complications will of course require inpatient management.

*In general terms:*

1. Attend to any immediate resuscitation as required:
2. Analgesia as clinically indicated.
  - Paracetamol is suitable for milder symptoms.
3. Heparin/ enoxaparin:
  - In moderate or more severe hospitalized cases, anticoagulation prophylaxis may be considered (after ruling out any hemorrhagic complications) - but this should be discussed with the O&G Unit.
4. Diuretics should be *avoided* due to the contracted intravascular volume.

*Management can be complex in severe cases and will need close input and coordination with both the ICU and the obstetrics units.*

5. Fluid management will involve:
  - Optimizing the intra-vascular volume with normal saline to:
    - ♥ Maintaining urine output of at least 30 mls per hour
    - ♥ Returning the hematocrit to normal.
  - A CVC and urinary catheter should be placed to help monitor fluid therapy.
7. ARDS may require CPAP
8. Paracentesis:
  - Ascites may cause significant discomfort, impairment to respiration and impairment of venous return (by compression of the IVC)
  - **Ultrasound guided** paracentesis should be considered in extreme cases of tense ascites.

Ultrasound-guided **culdocentesis** can be performed (even on an outpatient basis) in women with tense ascites

9. Cardiovascular collapse may require inotropic support in addition to fluid management.

*Disposition:*

**All actual or suspected cases of OHSS must be referred to the O&G Unit**

**Severe or critical cases will also need an ICU referral.**

*References*

1. Cristiano E Busso; Ovarian Hyperstimulation Syndrome in Up to Date Website, 1 June 2015.
2. Dr H. Smith et al, Prevention and Treatment of Ovarian Hyperstimulation Syndrome, Guidelines for the Westmead Hospital Department of Reproductive Medicine, 17 June 2005.

Dr J. Hayes

*Acknowledgements:*

Dr Mac Talbot

Annie Dixon (RN)

Dr G. Duke

Reviewed June 2015.