

International Federation of Fertility Societies
Global Standards of Infertility Care Standard

16

Ovarian Hyper Stimulation Syndrome (OHSS)

Recommendations for Practice

Name	Overview OHSS
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Introduction:

The goal of IFFS Practice Standards are to provide policy and decision-makers and the clinical and scientific community with a set of recommendations that can be used as a basis for developing or revising institutional or national guidelines on selected practice recommendations for infertility practice.

The document addresses minimal standards of practice but does not provide rigid guidelines but rather gives recommendations that provide the basis for rationalizing the provision of infertility services in view of the most up-to-date information available.

The intent of IFFS practice standards is to help improve access to, quality of, and safety of infertility and assisted conception services. These improvements must be made within the context of users' informed choice and medical safety. Because national situations and program environments vary so greatly, it is inappropriate to set firm international guidelines on infertility practice. However, it is expected that institutional and national programs will use these clinical standards documents for updating or developing their own infertility guidelines in the light of their national health policies, regulatory framework, needs, priorities and resources. Adaptation is not always an easy task and is best done by those well-acquainted with prevailing health conditions, behaviors, and cultures.

Rationale:

This standard provides guidance on the prevention, diagnosis, investigation and management

of ovarian hyperstimulation syndrome. This is the most serious life threatening and occasionally lethal complication of ART.

Standard 5 has addressed safety monitoring for ART emphasising the need for data collection and immediate reporting of this complication preferably to National registers.

A consensus needs to be reached on definition, grading and best approach to management which hopefully will lead to a better understanding of this syndrome.

IVF treatments are increasingly practiced around the world and about one million treatment cycles are currently estimated to be performed annually. Some four and a half million children have been born after IVF treatments, yet so far there is no clear consensus on success in terms of safety.

An international 4-level system is currently operating (clinics – national registers – regional registers – World Reports) to monitor efficacy and access and, most importantly, to monitor and report on the safety of these procedures i.e. immediate treatment complications for women as well as obstetrical and perinatal outcomes. The system is estimated to cover about 75% of all cycles performed, with large differences in different countries. A number of countries do have complete coverage but this is not the case everywhere. With cross border treatment increasingly commonplace the need for internationally agreed monitoring is further enhanced. Long-term follow-up of psycho-social and medical outcomes is much more complicated and is usually not done routinely by the clinics but rather through either specific (often multi-centred) research projects or on a national basis.

Knowledge about the safety of IVF is essential for all stakeholders in IVF: for patients (rational choices of treatments), for professionals (feedback on clinical policies), for industry (product developments) and for society (legal and economical considerations). Safety data on IVF are needed to build and maintain confidence.

Definition

A medical syndrome comprising ovarian enlargement and fluid accumulation in peritoneal and / or pleural or rarely pericardial cavities, following treatment with follicle stimulating hormone (FSH) and luteinising hormone (LH) or human chorionic gonadotrophin (hCG).

It may occur rarely with clomiphene citrate ovulation induction.

The risk of dying from OHSS in an IVF cycle has been estimated at 1:33,000 (Venn¹).

Classification

Since 1967 when initial classification was proposed there has been a lack of consensus on the definition of OHSS / severe OHSS so that information on evaluation of incidence and effective treatment of clinically significant OHSS is still difficult to assess. (Rizk and Aboulghar 1999²). Reported incidence varies from 0.6% to over 20%.

Pathophysiology

Following FSH and hCG the development of multiple follicles with very high levels of vascular endothelial growth factor (VEGF) produced by the ovaries induce vascularisation of the multiple corpora luteal, an increase in blood vessel permeability and transudation/leakage of fluid into intravascular compartments causing ascites , oedema and pleural effusion. This will result in a reduction in circulating blood volume, haemoconcentration, reduced renal perfusion and oliguria. Clinical manifestation may include hypotension, renal impairment, hepatorenal syndrome, thromboembolism and respiratory distress. Severe complications include deep venous thrombosis (DVT), pulmonary embolism (PE), arterial thrombosis, carotid vein thrombosis and stroke. Renal and respiratory failure, ovarian torsion and Ileus have all been reported.

Risk Factors

All women having ART using FSH are at risk. Incidence of OHSS is higher in women:

- Less than 33 years of age
- With low BMI
- LH:FSH ratio raised
- Polycystic ovary syndrome (PCOS)
- Hypogonadotrophic hypogonadism
- Previous OHSS
- Elevated baseline measurements of Ante Mullerian Hormone (AMH)

- Increased ovarian volume and preantral follicles on baseline ultrasound scan (Mathur³, Lee⁴)

High dose FSH, large number of follicles aspirated (>15) and rapidly rising or high oestrogen levels are all markers of OHSS in an IVF treatment cycle.

Clinical Presentation

Women may present early (3-7 days after HCG) or late (12-17 days after hCG and usually with a positive pregnancy test).

Clinical features include:

- Lower abdominal pain and bloating
- Nausea, vomiting and diarrhoea
- Shortness of breath, decreased exercise tolerance
- Vulval and peripheral oedema, ascites and pleural effusion

Examination should include weight, abdominal girth, state of hydration, cardiovascular and respiratory systems and abdominal examination.

Investigations

- Complete blood picture (PCV) - (haemoconcentration PCV > 0.45)
- Urea and electrolytes
 - Hyponatremia Na⁺ <130,
 - Mild elevation potassium
- LFTs, elevated
- Coagulation & D-dimers
 - Elevated D-dimers
 - Elevated fibrinogen
 - Reduced anti thrombin 3 level
- hCG
 - If >16 days following oocyte recovery.

The following when clinically indicated:

- Pelvic ultrasound scan
 - Doppler study if ovarian torsion suspected
 - Ovarian size
 - Ascites
- CXR
 - Pleural effusion assessment
 - Interstitial oedema
- CT - Angiogram
- VQ scan
 - Suspected pulmonary embolism

Prevention

Pre Treatment:

1. Reduction dose FSH

Particularly in women with PCOS/ PCO the starting dose of gonadotrophin ovarian stimulation take account of the increased risk of OHSS and, if known, the patient's previous response.

2. Metformin

In women with PCOS is associated in a significant reduction (Tso et al 2009 Cochrane⁵).

3. Use GnRH Antagonist

Reduces risk severe OHSS, hospital admissions and need for secondary interventions (Al-Inany HG et al Cochrane Review 2007⁶).

4. Aspirin

100mgs/day from Day 1 of ovarian stimulation until ultrasound evidence foetal heart, associated with reduction risk OHSS (Varnagy et al 2010⁷).

5. Ovarian Drilling

There is insufficient evidence to recommend this management.

During IVF cycle:

1. Coasting

There is need for further research (D'Angelo 2011 Cochrane Review⁸).

2. Cycle Cancellation

Avoidance hCG/LH administration in women at high risk reduces risk of OHSS at the expense of losing the cycle.

3. Recombinant LH versus Urinary HCG Trigger

No benefit has been demonstrated (Youssef et al 2011 Cochrane⁹).

4. GnRH agonist trigger in GnRH antagonist cycles

There is insufficient evidence of effective reduction OHSS in comparison to using hCG. A reduction in clinical pregnancy rate has been associated with this practice (Youssef Cochrane 2009. Engmann 2008¹⁰).

5. Reduction Trigger Dose

Reduction 10,000 IU to 5,000 IU reduces duration of action but was not associated with reduction risk OHSS (Kolibianakis et al 2007¹¹, Tsoumpou et al 2009¹²).

6. In vitro Maturation of Oocytes

The risk of OHSS is entirely avoided (Suikkari AM 2008¹³).

7. GnRH agonist trigger in GnRH antagonist cycles in combination with freeze all oocytes.

This combined treatment has been shown to significantly reduce and almost completely prevent OHSS in at risk patients (Griesingen et al 2011¹⁴).

8. Avoidance long acting GnRH stimulation in PCOS or patients with OHSS in previous cycle.

Post Trigger injection

1. I/V Albumin

There is limited evidence of benefit for I/V administration albumin at oocyte collection for prevention or reduction incidence of OHSS in high risk women (Youssef Cochrane Review 2010¹⁵).

2. Hydroxyethyl Starch

There was good evidence to support its use in the prevention of OHSS in high risk patients (Youssef Cochrane 2010¹⁵).

3. Cryopreservation all Embryos

Not enough evidence to show reduction OHSS in women at high risk. More research needed on effect pregnancy rates (D'Angelo Cochrane 2010¹⁶, Ferraretti 1999¹⁷)

4. Re-initiation GnRH Antagonist

In GnRH antagonist cycles following administration hCG trigger re-initiation GnRH antagonist can minimise progression of severe early OHSS. There is a need for more research (Lainas et al 2007¹⁸).

5. Carbergoline

A recent Cochrane review concluded that Cabergoline given in a dose of 0.5 mg daily from the time of egg retrieval reduces the likelihood of moderate OHSS (Tang et al¹⁹) although further evidence is required for larger trials this to be adopted in routine practice.

Management

OHSS is a self limiting condition. Treatment objectives are therefore to support the patient and prevent complications until vascular leakage resolves (days to weeks).

Outpatient management

This is suitable for women with mild OHSS characterised by:

- Mild symptoms / non tense ascites
- Can maintain oral intake 2-3L without vomiting
- Adequate urine output (non concentrated)
- No shortness of breath or pleural effusion
- No requirement for opiate analgesia
- No significant haemoconcentration (PCV < 0.45)
- Home support

Patient will require:

- Reassurance
- Encourage oral fluid intake
- Education to seek further help
 - + Increase abdominal bloating / pain
 - Nausea / vomiting / diarrhoea
 - Shortness of breath
 - Reduction urine output
 - Gentle mobilisation / avoid strenuous activity / intercourse.

In patient management

Admission is required if the following are present:

- Ascites / pain requiring opiate analgesia
- Inability to maintain oral intake 2-3 L/day
- Moderate to severe dehydration (PCV > 0.45)
- Tachycardia / hypotension / oliguria
- Abnormal biochemistry
 - $\text{Na}^+ < 135$, $\text{K}^+ > 5.0$
 - Abnormal LFT's
 - Serum albumin < 26

- Shortness of breath / pleural effusion
- Evidence thrombosis
- Difficulty mobilising / lack support at home
- Long distance from treatment centre

Monitoring

- Observation: 4 hourly temperature, pulse rate, BP, respiratory rate and oxygen saturation.
- Catheterise if oliguria or unsure fluid output with hourly urine charting.
- Daily abdominal girth, weight, tensesness ascites, respiratory assessment, calf tenderness.
- Daily blood test (12 hourly if oliguric)
 - CBP, D-dimers
 - Urea / serum electrolytes, LFT's
- Severe or unilateral abdominal pain consider ovarian torsion (Doppler ultrasound scan required urgently).

Therapy

1 Thromboprophylaxis

- TED stockings
- Low Molecular Weight Heparin (LMWH) 40mg s/c daily
- Mobilisation if possible

2 Analgesia and Antiemetics

- Paracetamol and opiates as required
- Avoid NSAID's (effect renal function / pregnancy)

3 Maintenance Intravascular Volume / Renal Function

- Initial bolus 500cc normal saline I/V if significant dehydration present.
- Restrict fluid intake to 2.0 – 2.5L daily (oral + I/V) and aim urine output > 30mls/hour.
- Prophylaxis for urinary tract infection if catheterised.
- I/V fluids

- Normal saline 100mls/hour initially
- If urine output < 30mls/hour for 2-4 hours commence 4% albumin (500mls at 100mls/hour and alternate with normal saline).
 - * *Albumin is often best given overnight as urine output is always reduced at night*
- If oliguria persists start 20% Albumin (100mls over 30 minutes).
- If no improvement consider ascites drainage to decompress renal artery.

Indication for Paracentesis

- Persistent oliguria
- Severe abdominal pain / tense ascites
- Poor chest ventilation or pleural effusions
 - **ascitic drain insertion under ultrasound guidance if possible*
- Drain 2L / 24 hours and clamp when daily drainage complete.

Maintenance of respiratory function

- Physiotherapy
- Decrease in oxygen saturation / respiratory compromise requires:
 - Arterial blood gases
 - Commence O2
 - Consider paracentesis
 - Respiratory physician review
 - (? *pulmonary embolism or infection*)
 - Consider drainage pleural effusion

Management of pregnancy

- hCG levels may not double every 48 hours (intravascular changes)
- avoid luteal hCG (exacerbation OHSS) and consider Crinone 8% or vaginal progesterone

- avoid pregnancy contraindicated medications
- termination pregnancy is rarely indicated

Transfer to High Dependency Unit / Intensive Care Unit

- Inability to maintain urine output / oliguria
- Respiratory compromise / significant pleural effusion
- Thromboembolic event

Recommendations for Practice

- OHSS is a serious complication which may be life threatening.
- OHSS is an avoidable complication with careful management.
- The incidence of OHSS requiring admission or invasive therapy e.g. paracentesis should be recorded as a quality indicator.
- PCOS patients should be considered for Metformin pre-treatment and the use of prophylactic aspirin should also be encouraged.
- High risk patients (in particular PCOS) should have low dose ovarian stimulation.
- High risk patients undergoing ovarian stimulation for IVF/ICSI should have ovarian suppression using GnRH antagonist as part of their stimulation regime as the risk of OHSS is reduced.
- The number of follicles developing during the stimulation phase is a key indicator of OHSS risk especially when there is a large number of small follicles coupled with a cohort of larger follicles.
- IVF cycle cancellation should be considered when the risk of OHSS during the cycle is high.
- The use of GnRH agonist trigger in GnRH antagonist cycle with 'freeze all' oocytes /embryos substantially reduces the risk of OHSS.
- The use of Hydroxyethyl starch rather than I/V albumin warrants further study and is not recommended.
- All other treatment measures (cryopreservation all embryos, re-initiation GnRH antagonist, Cabergoline, ovarian drilling) require further research before they can be recommended.

- Inpatient management must be considered when moderate-severe symptoms and signs are present particularly for patients residing a long distance from the treatment centre. In these cases management should include: appropriate expertise, intravenous fluids, anti coagulants, oxygen and respiratory support and facilities for paracentesis and thoracic drainage of pleural effusion.

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