MANAGEMENT OF OVARIAN HYPERSTIMULATION SYNDROME

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BACKGROUND:

- Ovarian hyperstimulation syndrome (OHSS) is an *exaggerated response* to ovulation therapy.
- The OHSS is typically associated with exogenous *gonadotropin* stimulation & is rarely observed with other agents (e.g. CC, letrozole).
- Clinicians who prescribe ovulation-inducing agents must be prepared to recognize & manage OHSS.
- OHSS is a *self-limiting disorder* that usually resolves spontaneously within several days, but may persist for longer periods, particularly in *conception* cycles.
- The syndrome is a *broad spectrum of clinical manifestations* from mild illness needing only observation to severe disease requiring hospitalization & intensive care.
- The syndrome is characterized by *ovarian enlargement* due to multiple ovarian cysts and an *acute fluid shift into the extravascular space*.
- Complications of OHSS include **ascites**, **hemo-concentration**, **hypovolemia**, and **electrolyte imbalances**.
- Because the prevalence of therapy employing ART is increasing, all physicians dealing with females in the reproductive age should be familiar with OHSS as it causes multi-organ dysfunction & may be fatal.
- Clinicians should be aware, and women informed, that pregnancies complicated by OHSS may be at increased risk of pre-eclampsia and preterm delivery.

HIGH RISK GROUP : *The incidence of OHSS is increased in the following conditions:*

RISK FACTOR
A). Primary risk factors (patient-related): 1. High basal AMH (>3.36 ng/ml (independent predictor). 2. Young age (< 33 years) 3. Previous OHSS (Moderate & severe cases / hospitalization) 4. PCO-like ovaries (> 24 antral follicles in both ovaries combined). **(B). Secondary risk factors (ovarian response related); On day of h C G trigger:** 1. High number of medium/large follicles (≥13follicles ≥ 11mm in diameter or > 11 follicles≥10 mm diameter) 2. High or rapidly rising E2 levels & high number of follicles (E2 5,000 pg/ml and/or≥18 follicles predictive of severe OHSS) 3. Number of oocyte retrieved (> 11predicts OHSS) 4. Elevated inhibin- B levels (Elevated levels on day 5 of gonadotropin stimulation, at oocyte retrieval and 3 days before) 5. hCG administration for luteal phase supp. --- *According to Martin et al (1994)**, if the pre-hCG treatment E2 is >6000mcg and /or if >30 follicles are present, the rate of severe OHSS approaches 80%*

CLINICAL PRESENTATION & CLASSIFICATION

According to time of onset, 2 main clinical forms of OHSS early & late;

1- **Early OHSS:** It occurs **within 9 days after oocyte retrieval** . It is correlated to ovarian response to exogenous hCG stimulation.

2- **Late OHSS**: It occurs **after 10 days of ovum pickup**, and correlated to endogenous hCG produced by implanting embryo.

CLASSIFICATION OF OHSS (Navot et al 1992)

OHSS stage	Clinical features	Lab. features
Mild	1. Abdominal distension/discomfort 2. Mild nausea/vomiting 3. Diarrhea 4. Ovarian enlargement 5-12cm	No important alterations
Moderate	1. Mild features + 2. Ultrasound evidence of ascites	1. Hematocrit>41% 2. WBC >15,000 3. Hypoalbuminemia
Severe	1. Moderate features+ 2. Clinical ascites, and/ or 3. hydrothorax, Severe dyspnea, 4. Oliguria/anuria 5. Intractable vomiting 6. Tense ascites 7. Low blood/central venous pressure 8. Rapid weight gain(>1kg/24hrs) 9. Syncope severe abdominal pain 10. Venous thrombosis	1. Hct >55% 2. WBC>25,000 3. Cr Cl<50ml/min 4. Cr >1.6mg/dl 5. Na+ <135mEq/L 6. K+ > 5mEq/L 7. Elevated liver enzymes
Critical	1. Anuria/ acute renal failure 2. Arrhythmia 3. Thromboembolism 4. Pericardial effusion 5. Massive hydrothorax 6. Arterial embolism 7. Adult RDS 8. Sepsis	Worsening of the previous finding

Prognosis (Lucidi,2013): (mortality= 1:400,000 to 1:500,000 stimulated cycles)

1-Mild and moderate cases = excellent prognosis
2-Severe cases = morbidity is clinically significant, and fatalities do occur. However, the prognosis is optimistic if adequate treatment is given.
3-Death from OHSS is largely due to: (a)hypovolemic shock, (b)Electrolyte imbalance, *(c) Hemorrhage, (d)Thromboembolism.*

PREVENTION OF OHSS

We should consider that.

- Complete prevention of OHSS is still not possible.
- Prevention strategies can be divided into two types—primary and secondary.
- **Primary prevention methods** ; the stimulation protocol is individualized (iCOS) after assessment of primary risk factors to classify patients as poor, normal, or high responders.
- **Secondary prevention methods**: are used in the presence of risk factors arising from an excessive response to ovarian stimulation

PRIMARY PREVENTION:

(A). Identification of high risk-group.

(B). Measures taken during stimulation cycle:

1. Reducing Exposure to Gonadotrpins:

Reducing the starting dose (e.g 75 U per day) and reduce the duration of stimulation. Chronic low dose step up protocol, mild stimulation protocols are options.

2-Using combined oral contraceptives:

-OCP for 28 days, GnRH-agonist started on day 21, overlapping OCP for 7days. On D3 of withdrawal bleeding low-dose (150 IU) hMG or rFSH is started & GnRH agonist dose reduced to half. Step-down gonadotropin adjustment is usually made.

-In some patients start gonadotropin at very low dose (37.5 IU/d) increased in a step-up fashion until follicles = 12 mm then step down.

3. GnRH Antagonist Protocols:

Used in high-risk patients with the advantages of lack of flare effect, no accompanying menopausal- like symptoms, no refractory period, reduced risk of ovarian cyst formation, shorter treatment cycle, reduced FSH consumption.

4. Avoidance of hCG for luteal phase support (LPS):

Luteal phase defect is the result of lowered endogenous LH release as a negative feedback from the supra-physiological levels of E2 & P of ovarian hyper-stimulation. Progesterone supplantation (with or without E2) is recommended.

5. In Vitro Oocyte Maturation (IVM):

In PCOS, and OHSS- high risk patient. IVM can be applied in patients undergoing COS for ICSI, where hCG was given when the leading follicle =12-14mm. Immature germinal vesicle (GV) stage oocyte retrieval without any ovarian stimulation followed by IVM to metaphase II stage represents an attractive strategy to eliminate the development of OHSS.

6. Insulin-Sensitizing Agents: 'metformin'

Metformin suppresses insulin levels & decreases ovarian theca cell androgen production, resulting in improved ovulatory and pregnancy rates. Metformin is effective insulin sensitizing agent with a good safety profile.

SECONDARY PREVENTION OF OHSS

5- Coasting
6- Reduced dose of hCG
7- Freeze all
8- Cancellation
9- Alternative triggering agents.
10- GnRH- agonist salvage

7. Luteal GnRH antagonist to prevent severe OHSS
8. IV albumen & hydroxyethy ethyl starch
1- Dopamine agonist
2- Glucocorticoid
3- Calcium gluconate infusion
4- Non-recommended strategies.

1- Coasting : It means withholding further gonadotropin stimulation & delaying hCG administration until E2 levels plateau or decrease significantly (Sher et al 1993).

2- Reduced Dose of hCG: Compared to the standard 10,000 IU, doses of 5,000 IU have been used successfully to trigger ovulation without impairing clinical outcome.

3- Cryopreservation of All Embryos (FREEZE ALL): -Entails normal progression of IVF/ICSI until OPU, followed by cryopreservation of embryos to be thawed & implanted at a later date when patient's hormones are not elevated.

4- Cycle Cancellation:-Cycle cancellation & withholding of hCG is the only guaranteed method for prevention of early OHSS .Despite the efficacy of this method, most physicians are reluctant to use it in IVF cycles because of the financial burden & psychological distress to the patient.

5- Alternative Agents for Triggering Ovulation:

a- GnRH agonist: - Used in gonadotropin-only in antagonist- stimulated cycles. Two or three ampoules (0.1mg) used for triggering ovulation.

b- Recombinant LH (rLH): - Despite the safety advantages of rLH in terms of OHSS reduction, however, reduced pregnancy rates and a poor cost/benefit ratio reduce its applicability in the clinical situation (Humaidan et al 2010)

6- GnRH Antagonist salvage: - administration of an *antagonist* to patients with elevated serum E2 at risk of developing OHSS may provide a means of interrupting the development or progression of the condition while salvaging the current treatment cycle.

7- Luteal GnRH antagonist to prevent severe OHSS:- cetrotide 0.25 mg SC given daily starting from day 5 after OPU for 4 doses in freeze all cycles will prevent severe OHSS in most cases.

8- Intravenous Albumin and Hydroxyethyl Starch: - Albumin may reduce the incidence of OHSS by binding to the vasoactive agents responsible for its development removing them from circulation &/or it increases the plasma osmotic pressure. Hydroxyethyl starch (HES) is a cheaper, potentially safer alternative to albumin and should be the 1st line treatment.

9- Dopamine Agonists: - Cabergoline reduces the occurrence of moderate-severe OHSS. It is unlikely to have a clinically relevant negative impact on clinical pregnancy or on the number of retrieved oocytes. A dose of 0.5 mg (1 tablet) is given daily for 8 days starting at day of triggering ovulation.

10- Calcium gluconate infusion: - Infusion with 10 ml of 10% calcium gluconate solution in 200 ml physiologic saline within 30 min of ovum pick up and continued thereafter on day 1, day 2 and day 3 proved to be as effective in preventing severe OHSS and decreases OHSS occurrence rates when used for high-risk patients.

11- Glucocorticoids. - Glucocorticoids and their derivatives have an inhibitory effect on the VEGF gene expression in vascular smooth muscle cells (Nauck et al 1998). An additional effect is the non-specific prevention of the inflammatory response and edema formation (Perretti 2000). Because the optimal dose is not agreed on, our practice is

adding 1 ampoule of dexamethasone 8 mg with the saline and calcium administered in number (9) above.

11-NON-RECOMMENDED OHSS- PREVENTION STRATIGIES

(a)-Follicular Aspiration before ovulation induction. (b)-Aromatase Inhibitors

TREATMENT OF OHSS

Patient Assessment:

History Taking: *(to classify disease severity):*
This should include a review of stimulation and a prediction of underlying risk based on age, onset of presentation, follicle number and size during stimulation, number of eggs retrieved, peak E2 level, and E2 level at trigger.

- The history should include an estimation of urine output and weight gain and should seek to identify symptoms such as abdominal pain, bloating, shortness of breath, and the ability to maintain oral hydration.

Physical examination:
- Should include measurement of vital signs, body weight, abdominal girth at the umbilicus, presence of ascites, pleural effusion, and signs of venous thromboembolic disease, such as unilateral increase in calf diameter. Caution should be taken with pelvic examinations to minimize the risk of trauma to enlarged ovaries.
- Initial laboratory investigations should screen for hemo-concentration with a hematocrit and/or hemoglobin measurement and urine specific gravity.

OUTPATIENT OR INPATIENT MANGEMENT?

Outpatient management: - is usually possible in women with mild & moderate OHSS. Women with severe disease may be considered for outpatient management if they are able to adhere to treatment and follow clinical instructions.

Inpatient management *: Women with OHSS who are :* [RCOG 2016]

- unable to achieve satisfactory pain control
- unable to maintain adequate fluid intake due to nausea
- show signs of worsening OHSS despite outpatient intervention
- unable to attend for regular outpatient follow-up
- have critical OHSS.

OUTPATIENT MANAGEMENT OF OHSS: [RCOG 2016]

- Women undergoing outpatient management of OHSS should be appropriately counselled and provided with information regarding fluid intake and output monitoring. In addition, they should be provided with contact details to access advice.
- Nonsteroidal anti-inflammatory agents should be avoided, as they may compromise renal function.
- Women with severe OHSS being managed on an outpatient basis should receive thromboprophylaxis with low molecular weight heparin (LMWH). The duration of treatment should be individualized, considering risk factors and whether or not conception occurs.
- Paracentesis of ascitic fluid may be carried out on an outpatient basis by the abdominal or transvaginal route under ultrasound guidance.
- There is insufficient evidence to support the use of gonadotrophin-releasing hormone antagonists or dopamine agonists in treating established OHSS.
- MONITOURING:

- Women with OHSS being managed on an outpatient basis should be reviewed urgently if they develop symptoms or signs of worsening OHSS. In the absence of these, review every 2–3 days is likely to be adequate.
- Baseline laboratory investigations should be repeated if the severity of OHSS is thought to be worsening. Hematocrit is a useful guide to the degree of intravascular volume depletion.

INPATIENT MANAGEMENT OF OHSS: [RCOG 2016]

- Multidisciplinary assistance should be sought for the care of women with critical OHSS and severe OHSS who have persistent hemoconcentration and dehydration.
- A clinician experienced in the management of OHSS should remain in overall charge of the woman's care.
- Analgesia and antiemetics may be used in women with OHSS, avoiding nonsteroidal agents and medicines contraindicated in pregnancy.
- Fluid replacement by the oral route, guided by thirst, is the most physiological approach to correcting intravascular dehydration.
- Women with persistent hemoconcentration despite volume replacement with intravenous colloids may need invasive monitoring and this should be managed with anesthetic input.
- Diuretics should be avoided as they further deplete intravascular volume, but they may have a role in a multidisciplinary setting if oliguria persists despite adequate fluid replacement and drainage of ascites.

- MOUNITORING: - Women admitted with OHSS should be assessed at least once daily. More frequent assessment is appropriate for women with critical OHSS and those with complications.

PATIENT MONITOURING: (Whelan et al 2000)

1- Admitted patients should be assessed by a physician at least once daily, with more frequent assessment in cases of critical OHSS.
2-Weight and urine specific gravity should be recorded daily.
3-Vital signs, urine output, and fluid balance should also be recorded. Urine output should be maintained at a minimum of 30 mL/hour.

4-Physical examination should assess hydration, cardiorespiratory status, degree of ascites, and signs of thromboembolism.
5-Daily monitoring of hemoglobin, hematocrit, creatinine, electrolytes, and albumin is useful to document disease progress.
6-A weekly measurement of liver enzymes may also be useful.

THERAPEUTIC MODALITIES:

1-PARACENTESIS: -patient with tense ascites. It will relieve pain, respiratory discomfort & improve oliguria. Insertion of an indwelling pigtail catheter under ultrasound guidance circumvents the need for multiple attempts at drainage and limits potential infectious complication (Whelan 2000).

Clinical resolution is achieved when paracentesis output starts to decrease as urine output increases. When ascites output is < 50 mL/ day the catheter can be removed (Rahami et al 1997).

2-CULDOCENTESIS: - Paracentesis by trans-vaginal ultrasound guidance can be done through the outpatient clinic (Abramov et al 1999). It is an alternative to paracentesis.

3-PLEURACENTESIS: - Drainage of ascites usually resolves a pleural effusion. Symptomatic pleural effusions that persist despite paracentesis can also be drained.

4-FLUIDS AND ELECTROLYTES: - Women should drink according to their thirst. In addition, IV hydration with a *crystalloid solution (100 to 150 mL/hr)* should be instituted until diuresis occurs. If clinical and laboratory findings indicate persistent intra-vascular volume depletion despite aggressive IV fluid hydration, *IV albumin (15 to20 mL/hr of 25% albumin over 4 hours)* should be initiated and repeated until hydration status improves (Fluker et al 2000). Diuretics should not be used as they can further deplete intra-vascular volume.

5-PAIN RELIEF: - Symptomatic relief of abdominal pain can be achieved with acetaminophen and if necessary oral or parenteral opiates. NSAIDs with antiplatelet properties should not be used because they may interfere with implantation and may also compromise renal function in women with severe OHSS (Navot et al 1992).

6-NAUSEA AND VOMITING: - Antiemetic agents considered to be safe in early pregnancy should be used to alleviate nausea and/or vomiting.

7-THROMBOPROPHYLAXIS: - Hospitalized patients should be considered at risk of thrombosis secondary to hemo-concentration and immobilization. Daily prophylactic doses of low-molecular weight heparin (e.g., dalteparin sodium 5000 IU/day) and use of thromboembolic deterrent stockings should be considered on admission and continued until discharge.

MANAGEMENT OF COMPLICATIONS:

- Renal failure, thromboembolism, pericardial effusion, and adult respiratory distress syndrome are potential life-threatening complications of OHSS.
- These conditions should be diagnosed early and managed by a multidisciplinary team possibly in an ICU setting.