In The Name of GOD

Ovarian Hyper Stimulation Syndrome

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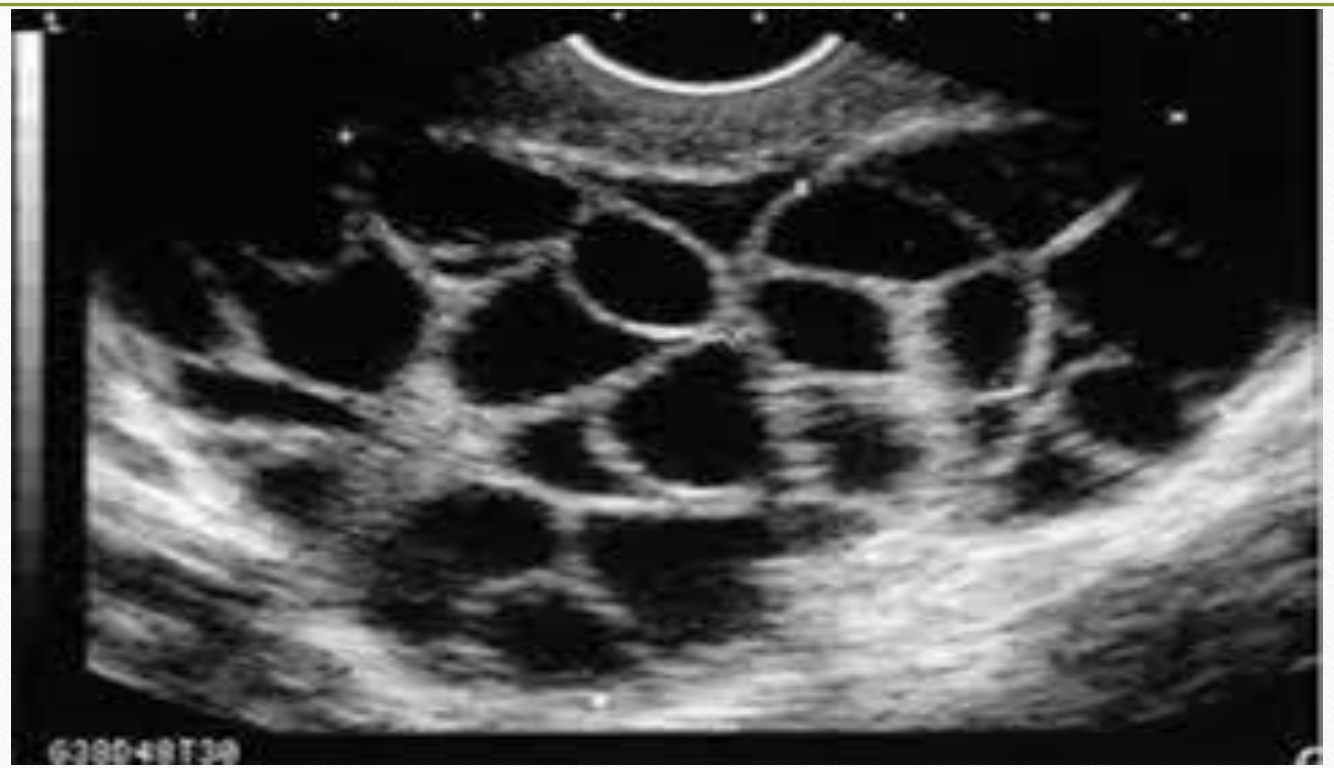

Definition

- **Ovarian hyperstimulation syndrome (OHSS)** is a serious and uncommon iatrogenic complication of assisted reproduction, caused by the use of gonadotrophins administered for controlled ovarian stimulation.
- However, it has to be mentioned that OHSS is rare without human chorionic gonadotropin (hCG) administration for ovulation triggering.

- Santos-Ribeiro S, et al 2015 Jul 13;32(7):1063–8. 2.

- Indeed, hCG, which is structurally and functionally similar to luteinizing hormone (LH), and has a longer half-life than LH (over 24 hours vs approximately 60 minutes for LH), seems to play a key role in the development of OHSS .
- The exposure of hyperstimulated ovaries to hCG represents a crucial event causing the production of proinflammatory mediators responsible for the clinical features of OHSS.

- Humaidan P et al, Repord Update. 2011 Jul;17(4):510–24

Pathophysiology & Incidence

- A variety of cytokines, proinflammatory mediators, and angiogenic molecules, such as vascular endothelial grow factor (VEGF), are likely to be involved in the pathogenesis of OHSS.
- The occurrence of ovarian enlargement with both local and systemic effects of inflammation mediators, including increased vascular permeability and a prothrombotic effect, are responsible for the clinical characteristics of OHSS.
- Moderate to severe OHSS occurs roughly in 1%–5% of stimulated cycles. Nevertheless, the real incidence is extremely difficult to estimate, since a strict consensus on the definition is lacking.
  - Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: Time for a change of practice? Hum Reprod Update. 2011 Jul;17(4):510–24

Pathophysiology
Common Physiologic Events Occurring in OHSS

- Include a spectrum of changes such as increased arteriolar vasodilation and capillary permeability in the region surrounding the ovaries and their vasculature.
- The crux seems to rely on a fine balance between proangiogenic and antiangiogenic factors present in follicular fluid.
- These alterations result in a phenomenon of fluid shifting from intravascular to extra-vascular spaces leading to a state of electrolyte unbalance called hypovolemic hyponatremia.

- Goldsman Mp et al, Fertil Steril. 1995;63(2):268–72. 9.
- Bergh PA, Navot D. J Assist Reprod Genet. 1992;9:429–38

- VEGF appears to be the chief among proinflammatory mediators, being mainly responsible for the development of OHSS, and being involved in follicular growth, corpus luteum function, angiogenesis, and vascular endothelial stimulation .
- Indeed, VEGF mediates the permeability of vascular endothelium in response to hCG, whose systemic levels are reported to positively correlate with the severity of the syndrome.
  - Neulen J, et al, J Clin Endocrinol Metab. 1995;80(6):1967

Other Systemic and Local Vasoactive Substances

- Interleukin-6, interleukin-1β, angiotensin II, insulin-like growth factor 1, transforming growth factor β, and the renin-angiotensin system .
- Finally, hCG and its analogues, oestrogens, oestradiol, prolactin, histamine, and prostaglandins, have all been implicated in OHSS.
  - Geva E, J. Fertil Steril. 2000;74: 429–38

Risk Factors: Demographic Factors (Age, BMI, Ethnicity, Reason for Infertility)

- The majority of OHSS cases occur in women who are less than 35 years old .
- Similarly, a lower BMI seems to correlate with an increased risk of the syndrome . On the other hand, several studies failed to replicate the same findings.
- With regard to the ethnicity, black race has been described as a predictive factor for OHSS .
- Enough evidence is showing a higher OHSS rate in women affected by polycystic ovary syndrome (PCOS).
- Black race has been described as a predictive factor for OHSS
  - Swanton A, Storey L, McVeigh E, Child T. IVF outcome in women with PCOS, PCO and normal ovarian morphology. Eur J Obstet Gynecol Reprod Biol. 2010;149(1):68–71.

Predictive for OHSS in Several Studies

- Ovarian reserve markers (AMH, AFC, inhibin A/B)
- Serum AMH levels have been shown to be predictive for OHSS (cut-off value 3.36 ng/mL).
  - Lee TH, Liu CH, Huang CC, Wu YL, Shih YT, Ho HN, et al. Serum anti-müllerian hormone and estradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproduction technology cycles. Hum Reprod. 2008;23(1):160–7

AMH levels in women who experienced OHSS

- Additionally, it has been reported that serum AMH levels in women who experienced OHSS were sixfold higher than age- and weight-matched controls.
- Among women with high AMH levels (>5 ng/mL), those who had extra-high levels of AMH (>10 ng/mL) had significantly higher rates (more than threefold) of OHSS.
  - Tal R, Seifer DBAm J Obstet Gynecol. 2014;211(1):59.e1–59.e8

A correlation has been found between AFC and OHSS

- A prospective analysis of 1012 first ART cycles described that the risk of OHSS increases from 2.2% into 8.6% when AFC is ≥24.
- Finally, to date, a correlation between serum (or follicular) inhibin A or B concentrations and the development of OHSS has not yet been demonstrated.
  - Ashrafi M,. Arch Gynecol Obstet. 2015 Nov 1;292(5): 1145–52.

Ovarian Stimulation Parameters (Follicles, Oocytes, Serum oestradiol levels)

- Multiple growing follicles during stimulation, high oestradiol levels, and elevated number of oocytes retrieved may help to identify those patients who are at risk to develop OHSS.
- Several studies have shown that a high number of growing follicles act as an independent predictor of OHSS.
- According to one study, a number of growing follicles ≥20 during ovarian stimulation significantly increases the risk of OHSS.
  - Danninger B. Hum Reprod. 1996;11(8):1597–9.
  - Jayaprakasan K, Hum Fertil. 2007 Sep;10(3):183–7.

Ovarian Stimulation Parameters (Follicles, Oocytes, Serum oestradiol levels)

- However, there is strong evidence that a count of ≥18 follicles having size ≥11mm diameter the day of triggering is predictive for high risk of severe.
- On the other hand, other data suggest a threshold of 13–15 follicles having a size of ≥10mm diameter prior to trigger for prediction of moderate OHSS.
  - byholm T,. Hum Reprod. 2000;15(7):1490–8
  - Tarlatzi TBJ Assist Reprod Genet. 2017 Oct 1;34(10):1341–5

Ovarian Stimulation Parameters (Follicles, Oocytes, Serum oestradiol levels)

- Finally, serum oestradiol levels were also significantly associated with OHSS.
- Most of these studies indicated that the mean serum oestradiol concentration in patients with OHSS was >3,500 pg/mL.
- However, it has to be mentioned that serum oestradiol levels >2,500 pg/mL are considered an important predictive factor for development of OHSS
  - Al-Shawaf T. Hum Reprod. 2001;16(1):24–30.

OHSS Represents in Unexpected Conditions

- Several cases of mild to severe OHSS have been reported in literature following ovulation induction with clomiphene citrate.
- On the other hand, OHSS may also be consequent to spontaneous conception especially in multiple or in molar pregnancies and also in association with hypothyroidism, pituitary tumors, as a familial predisposition and mutation in the FSHR gene.

- Lussiana C,. Gynecol Endocrinol. 2009;2

Late OHSS

- With the term "early" is defined that type of OHSS usually presenting in seven days from the trigger injection; this type of OHSS is commonly associated with an excessive ovarian response.
- The term "late" indicates OHSS occurring 10 or more days after the trigger injection; this is the result of endogenous hCG derived from an early pregnancy.

- Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, Kolibianakis E, et al. ESHRE guideline: Ovarian stimulation for IVF/ICSI. Hum Reprod Open. 2020 Feb 1;2020(2):1–13.

Late OHSS

- Late OHSS tends to be more prolonged and severe than the early form.
- However, it should be pointed out that OHSS is a self-limiting condition especially in patients who do not become pregnant with typical resolution of symptoms at the time of the next menstrual period.

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Late OHSS

- Conversely, in patients who do conceive, the ovaries continue to be stimulated by the increasing hCG levels with symptoms that may last until the end of the first trimester.
- Moreover, it has to be mentioned that multiple pregnancies represent a risk factor for the late form due to the higher levels of HCG produced with consequent secretion of higher amounts of vasoactive factors.

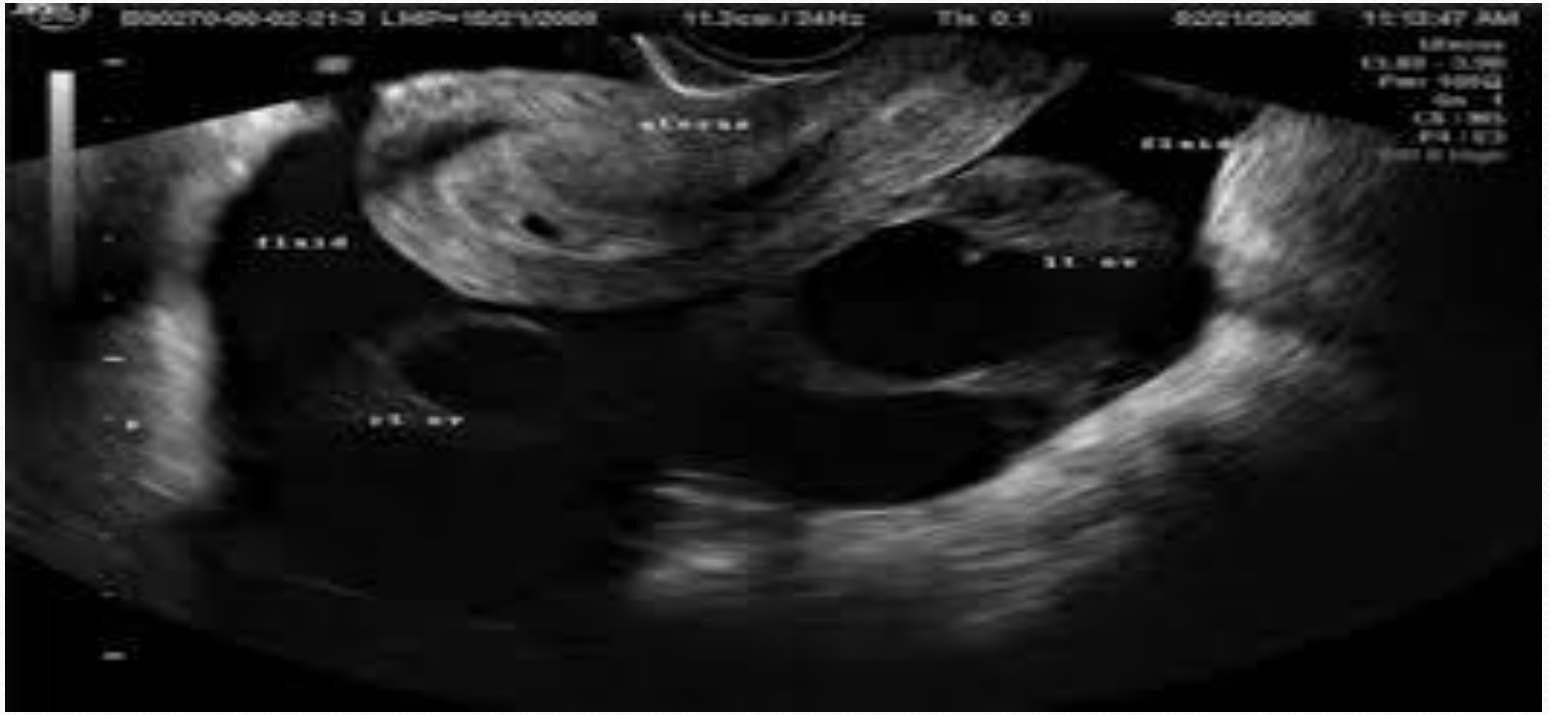


TABLE 69.1 Initial Assessment

Questions Regarding the History

- When did the symptoms occur? (Early or late onset relative to trigger)
- Which medication has been used for trigger? (hCG or GnRH agonist)
- How many follicles did you have on final monitoring scan?
- How many oocytes have been collected?
- Were embryos replaced and how many?
- Polycystic ovary syndrome diagnosis?

Symptoms

- Abdominal bloating
- Abdominal discomfort/pain, need for analgesia
- Nausea and vomiting
- Breathlessness, inability to lie flat or talk in full sentences
- Reduced urine output
- Leg swelling
- Vulval swelling
- Associated comorbidities such as thrombosis

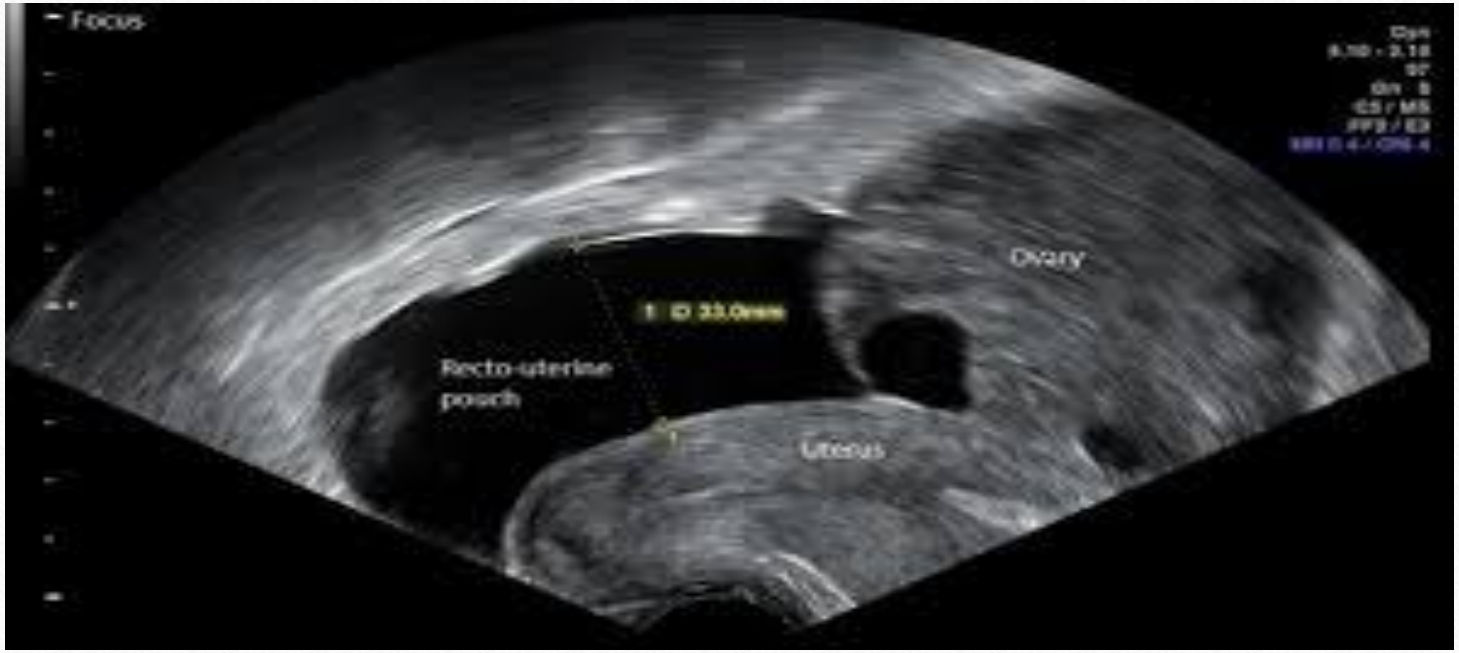
Classification of OHSS symptoms.

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

Note: Hct = hematocrit; WBC = white blood cell; CrCl = creatinine clearance; Cr = creatinine; Na+ = sodium; K+ = potassium.

Adapted from Navot D, Bergh PA, Laufer N (Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1992;58:249-61). Terms of use: Fiedler K, Ezcurra D (Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. Reprod Biol Endocrinol 2012;10:32. © 2012 Fiedler and Ezcurra; licensee BioMed Central Ltd. This work is licensed under a Creative Commons Attribution 2.0 Generic License: http://creativecommons.org/licenses/by/2.0. It is attributed to Klaus Fiedler and Diego Ezcurra, and the original version can be found at http://rbej.biomedcentral.com/articles/10.1186/1477-7827-10-32#CR9).

Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe OHSS. Fertil Steril 2016.


Focus
ovary
Recto-uterine
pouch
uterus

Assessment

- Assessment by clinicians may be focused on the evaluation of blood parameters such as full blood count, serum electrolytes, and osmolality.
- Indeed, reduced serum osmolality and sodium combined with elevated haematocrit is indicative of OHSS.
- On the other hand, pelvic ultrasound and, eventually, abdominal imaging may be of high clinical relevance to make the diagnosis.
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Patient Management
The scope of the initial assessment

- The scope of the initial assessment is to establish the grade and the severity of OHSS. In the first instance, telephone assessment may represent a useful modality to establish the presence and the grade of OHSS.
- Recent history of the patient and if abdominal pain, shortness of breath or impression of reduced urine output have occurred.
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Patient Management

- With regard to mild stages of OHSS, they may be managed on an outpatient basis. No specific evidence is existent regarding fluid intake; in view of this, it should be recommended to thirst with at least 1 liter/day.
- Fluid input–output charts could be registered by the patients themselves. Urine output of less than 1000 mL per 24 hours or a positive fluid balance of greater than 1000 mL over 24 hours should prompt medical review to assess severity.

Patient Management

- Considering pain relief therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may impair renal function in OHSS patients, whereas paracetamol and oral opiates including codeine can be safely administered.
- Women with severe OHSS are at increased risk of thromboembolism; in this view, although there are no trials on this argument, thromboprophylaxis should be provided for these women.
- Finally, it has to be mentioned that ultrasound-guided paracentesis may represent a safe alternative to hospitalization in patients with severe OHSS.
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The Patients with Severe OHSS

- In patients with severe OHSS who have persisting dehydration and haemoconcentration despite an adequate fluid replacement, **invasive hemodynamic** monitoring may be needed with input from **anesthetic/intensive care colleagues**.
- Intensive care may also be required for women with critical OHSS showing specific complications such as thromboembolism, acute respiratory distress syndrome (ARDS), and renal failure.

TABLE 69.5 Signs of OHSS Increased Severity

Increasing abdominal distension and pain
Shortness of breath
Tachycardia or hypotension
Reduced urine output (less than 1000 mL/24 hours) or positive fluid balance (more than 1000 mL/24 hours)
Weight gain and increased abdominal girth
Increasing haematocrit (>45%)

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TABLE 69.6 Conditions Requiring Patient Admission to the Hospital

No satisfactory pain control
No adequate fluid intake due to nausea
Signs of worsening OHSS despite outpatient intervention
Inability to attend for regular outpatient follow-up
Critical OHSS

Monitoring of Women with OHSS

- Monitoring of women with OHSS should have the scope to intercept changes in the severity of the condition and complications at an early stage.
- Daily check-up of body weight, abdominal girth, fluid intake, and fluid output should be performed,
- along with blood samples reporting full blood count, hematocrit, serum electrolytes, osmolality, and liver function tests.
- Depending on the clinical features, arterial blood gases, ECG, chest X-ray, and other imaging may be necessary.
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Signs of Worsening OHSS

- Include increasing abdominal girth, weight gain, oliguria with positive fluid balance, and elevated hematocrit.
- Conversely, recovery is undelighted by reduction in abdominal girth and body weight as well as normalization of diuresis and hematocrit.
- On the other hand, it seems that C-reactive protein levels correlate with other markers of OHSS such as abdominal girth and weight and may have a role in monitoring severity.
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Oral route

- Physiological fluid replacement by the oral route, guided by thirst, represents the first approach to correct dehydration.
- Moreover, it seems that excessive intravenous fluid therapy with crystalloids may be dangerous as it may potentially worsening the ascites in the presence of increased capillary permeability.
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Women who are not able to maintain adequate oral intake

- However, when persisting hemoconcentration and acute dehydration, initial correction with crystalloids and/or colloids may be useful for those women who are not able to maintain adequate oral intake.
- Human albumin solution 25% may be used as a plasma volume expander in doses of 50–100 g, infused over four hours and repeated 4 to 12-hourly.
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Hydroxyethyl starch solution (HES)

- Six per cent hydroxyethyl starch solution (HES) has been compared to human albumin as colloid solutions for treatment of severe OHSS in 16 patients.
- It seems that patients who received HES had shorter duration of hospital stay and higher urine output than women treated with albumin.

HES

- Moreover, fewer abdominal paracenteses and pleural thoracenteses were needed compared to patients who received albumin. No difference in adverse effects was reported.
- These results underlined that 6% HES may be superior to albumin as a colloid solution for the treatment of severe OHSS.

- Abramov Y, Fatum M, Abrahamov D, Schenker JG. Hydroxyethylstarch versus human albumin for the treatment of severe ovarian hyperstimulation syndrome: A preliminary report. Fertil Steril. 2001;75(6):1228–30

Ascites/Culdocentesis

- **Ascites/culdocentesis** — Although transabdominal paracentesis is reported to be successful , most in vitro fertilization (IVF) centers are more experienced with transvaginal aspiration of the ascitic fluid from the cul-de-sac, guided by TVUS. Ultrasound-guided culdocentesis is often performed (even on an outpatient basis) in women with tense ascites, orthopnea, rapid increase of abdominal fluid, or any other sign that may indicate progression of illness .
- Removal of ascitic fluid provides symptomatic relief; women without other complications can then continue to be monitored as outpatients.
- The volume of fluid to be removed is not well established, but after aspiration of 500 mL of ascitic fluid, patients typically report resolution of abdominal discomfort. In one report of 19 women with OHSS, after aspiration of 2000 mL of ascites, a reduction in intra-abdominal pressure and renal artery resistance was seen, followed by an increase in urine output . Removal of more than 4 liters of fluid is not recommended.
- Blind paracentesis should not be done, because of the potential risk of bowel or vessel puncture.
- Uptodate 2024

Oliguria despite adequate fluid replacement

- Oliguria despite adequate fluid replacement may in some cases respond to paracentesis, however dopamine infusion or oral docarpamine administration is also described in literature to treat severe OHSS.
  - Maslovitz S, Jaffa A, Eytan O, Wolman I, Many A, Lessing JB, et al. Renal blood flow alteration after paracentesis in women with ovarian hyperstimulation. Obstet Gynecol. 2004 Aug;104(2): 321–6

Diuretics

- With regard to use for management of fluid balance in women with OHSS, it seems that there is a risk of worsening hypovolemia if diuretics are administered without correcting dehydration.

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Careful use of diuretics

- However, should be recommended in women who maintain the condition of oliguria despite an adequate fluid replacement,
- especially if any tense ascites that may have been contributing to oliguria has been drained by paracentesis.

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Thromboembolism

- Severe hypovolemia may rarely lead to life-threatening risk for arterial or venous thromboembolism, hence, prophylactic anticoagulation is warranted for patients with severe OHSS from the time of diagnosis through the first trimester of pregnancy.

Prophylaxis for thromboembolic events

- **All** hospitalized patients with OHSS.
- Women with OHSS being managed as outpatients with two to three additional risk factors (in addition to OHSS):

age >35 years,
obesity, immobility, personal or family history of thrombosis, thrombophilia, and pregnancy.

- For those in whom bed rest is suggested, an intermittent pneumatic compression device is typically recommended.
- We use prophylactic low molecular weight heparin, 20 mg subcutaneously every 12 hours, or heparin 5000 units subcutaneously every 12 hours.

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Prevention of OHSS

Primary Prevention: The use of a GnRH antagonist protocol

- Several studies described that the use of gonadotropin-releasing hormone (GnRH) antagonists protocols results in a lower incidence of OHSS compared with protocols that use a GnRH agonist.
- Indeed, it seems that the mechanism of reduction in circulating oestradiol levels seen with GnRH antagonist suppression would be in favour to the lower risk of OHSS.

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GnRH antagonist protocol should be recommended for

- PCOS/polycystic ovary morphology (PCOM) patients,
- And for those who are predicted high responders.

- Firouzabadi RD, Ahmadi S, Oskouian H, Davar R. Comparing GnRH agonist long protocol and GnRH antagonist protocol in outcome the first cycle of ART. Arch Gynecol Obstet. 2010 Jan;281(1):81–

GnRH antagonist protocol

- A Cochrane review analyzing data from 29 randomized controlled trials (RCTs) showed a statistically significant lower incidence of OHSS in the GnRH antagonist group (odds ratio [OR] 0.43, 95% CI 0.33–0.57) and no difference in live birth rates compared to women who underwent GnRH agonist protocol.

- Al-Inany HG, Youssef MA, Aboulghar M, Broekmans FJ, Sterrenburg MD, Smit JG, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev. 2011;(5):CD001750

Addition of clomiphene to controlled ovarian stimulation

- With regard to the in antagonist protocols, several studies described a reduction of OHSS risk.
- However, the heterogeneity of the population included (i.e. patients who underwent minimal stimulation protocols) led to a difficult interpretation of the results.
  - Al-Inany HG/et al/Cochrane Database Syst Rev. 2011;(5):CD001750

Secondary Prevention: Agonist trigger for final oocyte maturation prior to retrieval

- Bodry et al. evaluated a cohort of oocyte donors over 4052 stimulation cycles in which hCG or GnRH agonist was administered on physician discretion.
- In accordance with other reports, moderate/severe OHSS occurs less frequently in those women receiving GnRH agonist trigger compared with hCG (0% [0/1519] vs 0.87% [22/2533], respectively).
  - Orvieto R, Rabinson J, Meltzer S, Zohav E, Anteby E, Homburg R. Substituting HCG with GnRH agonist to trigger final follicular maturation - A retrospective comparison of three different ovarian stimulation protocols. Reprod Biomed Online. 2006;13(2):198–201.

Fresh Embryo Transfer

- However, for the lower incidence of OHSS in fresh autologous cycles reported in a Cochrane review published in 2014 summarizing the results of 17 RCTs, the authors also reported a lower live-birth rate (OR 0.47, 95% CI 0.31–0.70; five RCTs, 532 women, moderate-quality evidence) in fresh autologous cycles.
  - Youssef MAFM, et al/. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology. Cochrane Database Syst Rev. 2014;2014:CD008046.

The Mechanism of LBR

- The mechanism by which live birth rate is impaired, is probably based on the rapid decrement and dramatic post-luteal drop in LH support compared to hCG for maturation, this results in luteal phase insufficiency.

- Along this line, the strategy of co-administration of GnRH agonist trigger with low dose hCG (1000 IU, 500 IU, or 250 IU every third day after retrieval) for luteal support may restore pregnancy rates and still reduce OHSS with a trend towards higher incidence of moderate OHSS with the 1000 IU dosing compared to the lower doses.
  - Castillo JC, Dolz M, Bienvenido E, Abad L, Casan EM, Bonilla Musoles F. Cycles triggered with GnRH agonist: Exploring low-dose HCG for luteal support. Reprod Biomed Online. 2010;20(2):175–81

HCG after the oocyte retrieval

- Moreover, an RCT of 384 patients showed that GnRH agonist trigger in association with a single bolus of 1500 IU of hCG after the oocyte retrieval decreased OHSS in high-risk patients.
- However, there was an increased risk of moderate-to-late onset of OHSS when patients received a second bolus of 1500 IU (one the day of retrieval and one the subsequent day).

- Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO, et al. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: Two prospective randomized controlled multi-centre studies in IVF patients. Hum Reprod. 2013;28(9):2511–21

Tertiary Prevention: Co-adjuvant treatments Aspirin or Metformin

- The use of aspirin for OHSS prevention has been investigated by two randomized trials.
- These studies found a lower incidence of OHSS in patients treated with a daily dose of 100 mg aspirin from the first day of stimulation until the day of the pregnancy test/detection of embryonic cardiac activity.
  - Revelli A, Dolfin E, Gennarelli G, Lantieri T, Massobrio M, Holte JG, et al. Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: A prospective, randomized study. Fertil Steril. 2008 Nov;90(5):1685–91.

Mechanism at the base of OHSS consists

- Indeed, mechanism at the base of OHSS consists in a releasing of substances (histamine, serotonin, platelet-derived growth factor, lysophosphatidic acid) due to an activation of platelet by VEGF.
- Given this, aspirin has been suggested to have a potential role in reduction of OHSS risk.

Metformin

- With regard to the metformin, its action of improvement of intraovarian hyperandrogenism contributes to the reduction of estradiol secretion due to the decrement of the number of periovulatory follicles.
  - Várnagy Á, Bódis J, Mánfai Z, Wilhelm F, Busznyák C, Koppán M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. Fertil Steril. 2010;93(7):2281–4.

- Several studies have shown that metformin at the onset of downregulation during ovarian stimulation until oocyte retrieval in PCOS women reduces the risk of OHSS.
- In accordance, several RCTs and a systematic review have supported this conclusion. However, this effect has not yet been demonstrated in patients with PCOM only and those who are of standard weight.

- Tang T, ET AL. The use of metformin for women with PCOS undergoing IVF treatment. Hum Reprod. 2006;21(6):1416–25
- Qublan HS, et al. Metformin in the treatment of clomiphene citrate-resistant women with polycystic ovary syndrome undergoing in vitro fertilisation treatment: A randomised controlled trial. J Obstet Gynaecol. 2009;29(7):651–5

Relcovaptan

- Vasopressin-induced vascular endothelial growth factor secretion blockade Relcovaptan is a non-peptide vasopressin receptor antagonist able to contrast the VEGF action by adjusting vascular smooth muscle proliferation and vasoconstriction.
- A study on hyperstimulated rat models, treated with relcovaptan showed lower concentrations of the VEGF-A in the peritoneal fluid, lower weight gain, and decreased number of corpora lutea.

- Cenksoy C, Cenksoy PO, Erdem O, Sancak B, Gursoy R. A potential novel strategy, inhibition of vasopressin-induced VEGF secretion by relcovaptan, for decreasing the incidence of ovarian hyperstimulation syndrome in the hyperstimulated rat model. Eur J Obstet Gynecol Reprod Biol. 2014;174(1):86–90

Withholding gonadotropins

- It seems that coasting is associated with a lower risk of OHSS without compromising the pregnancy rate.
- However, this evidence is not supported by a systematic review of four RCTs which described that the risk of OHSS is not decreased with coasting.

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Dopamine-receptor agonist treatment

- Treatment with dopamine-receptor agonist has been supposed to result in a decreasing VEGF production with consequent reduction of OHSS symptoms and grade,
- especially for patients with moderate OHSS.

Dopamine-receptor agonist treatment

- The incidence of OHSS was significantly lower in women treated with cabergoline compared with no treatment (RR 0.38, CI 0.29–0.51, P < .00001), without any impact reported on pregnancy rates.

- Álvarez C, Martí-Bonmatí L, Novella-Maestre E, Sanz R, Gómez R, Fernández-Sánchez M, et al. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab. 2007;92(8):2931–7.
- Tang H, Mourad SM, Wang A, Zhai S, Di, Hart RJ. Dopamine agonists for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2021;2021: CD008605.

THREE WAYS OF ADMINISTERATION

- With regard to dosage and timing of administration, most of the studies suggested the use of cabergoline 0.5 mg orally daily for seven or eight days starting on the day of oocyte pickup or hCG trigger.
- On the other hand, other studies gave oral cabergoline 0.5 mg per day for three weeks beginning on the day after the oocyte retrieval.
- Finally, 0.25 mg of cabergoline daily for eight days from the day of HCG administration has been also proposed.
- Mild side effects such as stomach upsets, feeling sick, or dizziness must be taken into account

- Carizza C, Abdelmassih V, Abdelmassih S, Ravizzini P, Salgueiro L, Salgueiro PT, et al. Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: A prospective randomized study. Reprod Biomed Online. 2008;17(6):751–5

Albumin administration

- Albumin and calcium administration The rationale of using albumin as method to prevent of OHSS relies on the fact that it has low molecular weight as well as an average half-life of 20 days, acting as an increaser of plasma oncotic pressure and contrasting the permeability effect of angiotensin II.
- Moreover, it binds vasoactive substances, such as factors related to the renin-angiotensin system and VEGF.

Albumin administration

- However, contrasting data exist about the role of albumin in the prevention of OHSS.
- Older studies demonstrated a trend towards the positive effect of human albumin administrated at the time of oocyte retrieval, reducing the incidence of moderate-to-severe OHSS compared with no treatment.
- However, recent evidence failed to replicate the same findings.
  - Isikoglu M, Berkkanoglu M, Senturk Z, Ozgur K. Human albumin does not prevent ovarian hyperstimulation syndrome in assisted reproductive technology program: A prospective randomized placebo-controlled double blind study. Fertil Steril. 2007 Oct;88(4):982–5.

Pregnancy rate

- In addition, two systematic reviews concluded that albumin is not effective in preventing OHSS also reporting a significant lowering of pregnancy rate in patients who received albumin around oocyte retrieval compared with no treatment.
- It is also important to remember that the administration of albumin (as blood-derived product) may cause allergic reactions, anaphylactic reactions as well as rare but possible transmission of viral or unidentified diseases.

- ee BC, Suh CS, Kim YB, Kim SH, Choi YM, Kim JG, et al. Administration of intravenous albumin around the time of oocyte retrieval reduces pregnancy rate without preventing ovarian hyperstimulation syndrome: A systematic review and metaanalysis. Gynecol Obstet Invest. 2010;70:47–54
- Venetis CA, Kolibianakis EM, Toulis KA, Goulis DG, Papadimas I, Tarlatzis BC. Intravenous albumin administration for the prevention of severe ovarian hyperstimulation syndrome: A systematic review and metaanalysis. Fertil Steril. 2011;95(1):188–96, 196.e1-3

Transfer Cycles vs. FREEZ ALL STRATEGY

- Transfer cycles, which may be responsible for late-onset OHSS symptoms and its longer duration.
- A small RCT reported the successful use of elective cryopreservation as method to prevent OHSS, compared to albumin in preventing mild, moderate, and severe OHSS in high-risk women.
  - Shaker AG, Zosmer A, Dean N, Bekir JS, Jacobs HS, Tan SL. Comparison of intravenous albumin and transfer of fresh embryos with cryopreservation of all embryos for subsequent transfer in prevention of ovarian hyperstimulation syndrome. Fertil Steril. 1996;65(5):992–6

Use of IV Calcium

- Similarly, the use of IV calcium (10 mL of 10% calcium gluconate in 200 mL normal saline) around the day of oocyte retrieval and thereafter has been investigated as a strategy to reduce OHSS.
- Calcium is described to inhibit the secretion renin mediated by cAMP resulting in a reduction of angiotensin II and subsequent decrease of VEGF production.

Use of IV Calcium

- A RCT compared the use IV calcium and normal saline in 200 women at risk for OHSS reporting higher incidence of moderate and severe OHSS in women treated with normal saline, without impact on clinical pregnancy or ongoing pregnancy rate between the groups.
- In addition, evidence suggests that IV calcium is as effective as cabergoline in lowering the OHSS risk in PCOS women and in its prevention.

- El-Khayat W, Elsadek M. Calcium infusion for the prevention of ovarian hyperstimulation syndrome: A double-blind randomized controlled trial. Fertil Steril. 2015;103(1):101–5

Letrozole

- High serum estrogen levels are associated with an increased risk of OHSS.
- Letrozole, a nonsteroidal aromatase inhibitor, impedes the conversion of androgens into estrogens by inhibiting aromatase activity.
- Recent evidence suggests that using letrozole after oocyte retrieval may reduce estrogen concentrations and potentially decrease the incidence of OHSS.

- Mai Q, Hu X, Yang G, Luo Y, Huang K, Yuan Y, et al. Effect of letrozole on moderate and severe early-onset ovarian hyperstimulation syndrome in high-risk women: A prospective randomized trial. Am J Obstet Gynecol. 2017 Jan 1;216(1):42.e1–42.e10.

- To date, the guideline for “Prevention and Treatment of moderate and severe ovarian hyperstimulation syndrome” do not mention Letrozole as agent for OHSS prevention.

- Pfeifer S, Butts S, Dumesic D, Fossum G, Gracia C, La Barbera A, et al. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: A guideline. Fertil Steril. 2016 Dec 1; 106(7):1634–47

Investigated the effects of different doses of letrozole on the incidence of OHSS

- In high-risk IVF patients Daily doses of 2.5 mg, 5.0 mg, and 7.5 mg for five days were shown to decrease estrogen levels and VEGF.
- While the 2.5 mg and 5 mg doses slightly reduced OHSS incidence, the higher dose of 7.5 mg resulted in a significant reduction, indicating its effectiveness in limiting OHSS .
- Additionally, letrozole was compared with aspirin for early OHSS prevention, with results favoring letrozole as it was more effective than aspirin in decreasing moderate and severe early-onset OHSS. This study suggested that OHSS might be caused by a luteolytic effect rather than modulation of VEGF

- Wang YQ, Wang J, Wang WM, Xie QZ, Yan WJ, et al. [Luteal letrozole administration decreases serum estrogen level but not the risk of ovarian hyperstimulation syndrome]. Beijing Da Xue Bao Yi Xue Ban. 2013 Dec 18;45(6):869–72.

Luteal phase support

- Focus on Luteal phase support (LPS) represents a crucial step in IVF cycles followed by fresh embryo transfer, with a wealth of studies investigating its efficiency, route, and duration.
- Although different routes, alone or in combination, have been proposed during the last decade, the vaginal route seems to be the preferential route for LPS.

Guardo D, Midassi F, Racca H, Tournaye A, Vos D, Blockeel M. Luteal phase support in IVF: Comparison between evidence-based medicine and real-life practices. Front Endocrinol (Lausanne). 2020 Aug 18;11:500

Luteal phase supplementation

- On the other hand, there is a tendency to abandon the use of hCG as an agent for luteal phase supplementation.
- In this context, the results of a Cochrane meta-analysis showed that hCG is not superior to progesterone for LPS; moreover, analysis of pooled data pointed toward a higher risk of OHSS when hCG was administered in the luteal phase.
- Considering this, the use of hCG for LPS should be avoided especially for those women at high risk for OHSS. Conversely, the option of LPS with sole GnRH agonist has been proposed as a possible approach for LPS in patients having elevated risk for OHSS.

- van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015;2015(7):CD009154

Prevention of moderate and severe ovarian hyperstimulation syndrome: a guideline (2023)

ASRM 2023

- It is recommended to counsel patients with elevated antimullerian hormone levels, polycystic ovary syndrome (PCOS), and anticipated high oocyte yields that they are at increased risk for ovarian hyperstimulation syndrome (OHSS).
- Interventions to reduce OHSS risk should be focused on this patient population. (Strength of evidence: A; strength of recommendation: strong).
- It is recommended to employ ovarian stimulation protocols using gonadotropin-releasing hormone (GnRH) antagonists over protocols using GnRH agonists when there is a concern for OHSS. (Strength of evidence: A; strength of recommendation: strong).
- It is recommended to dose gonadotropins based on individualized ovarian reserve testing to decrease the risk of OHSS. (Strength of evidence: B; strength of recommendation: moderate).

ASRM 2023

- It is recommended to consider lowering the starting dose of gonadotropins and/or supplementing with oral ovulation-inducing medications (clomiphene citrate and/or letrozole) to decrease the risk of OHSS. (Strength of evidence: B; strength of recommendation: moderate).
- Coasting is generally not recommended as a primary strategy to reduce the risk of moderate-to-severe OHSS. However, when other more effective strategies are not available to reduce the risk of OHSS, coasting in combination with cabergoline and a freeze-only strategy may mitigate the risk. (Strength of evidence: C; strength of recommendation: weak)
- It is recommended to use a GnRH agonist to trigger oocyte maturation as a first-line strategy to reduce the risk of moderate-to-severe OHSS. (Strength of evidence: A; strength of recommendation: strong).

ASRM 2023

- It is recommended to add adequate luteal support when using a GnRH agonist as a trigger and planning a fresh embryo transfer. (Strength of evidence: A; strength of recommendation: strong)
- It is not recommended to use a lower dose for the human chorionic gonadotropin (hCG)-only trigger as a strategy to reduce the risk of moderate-to-severe OHSS. (Strength of evidence: C; strength of recommendation: weak).
- In patients at risk for moderate-to-severe OHSS, it is recommended to start a dopamine agonist such as cabergoline on the day of the hCG trigger or soon thereafter and continue for several days. (Strength of evidence: A; strength of recommendation: strong)

ASRM 2023

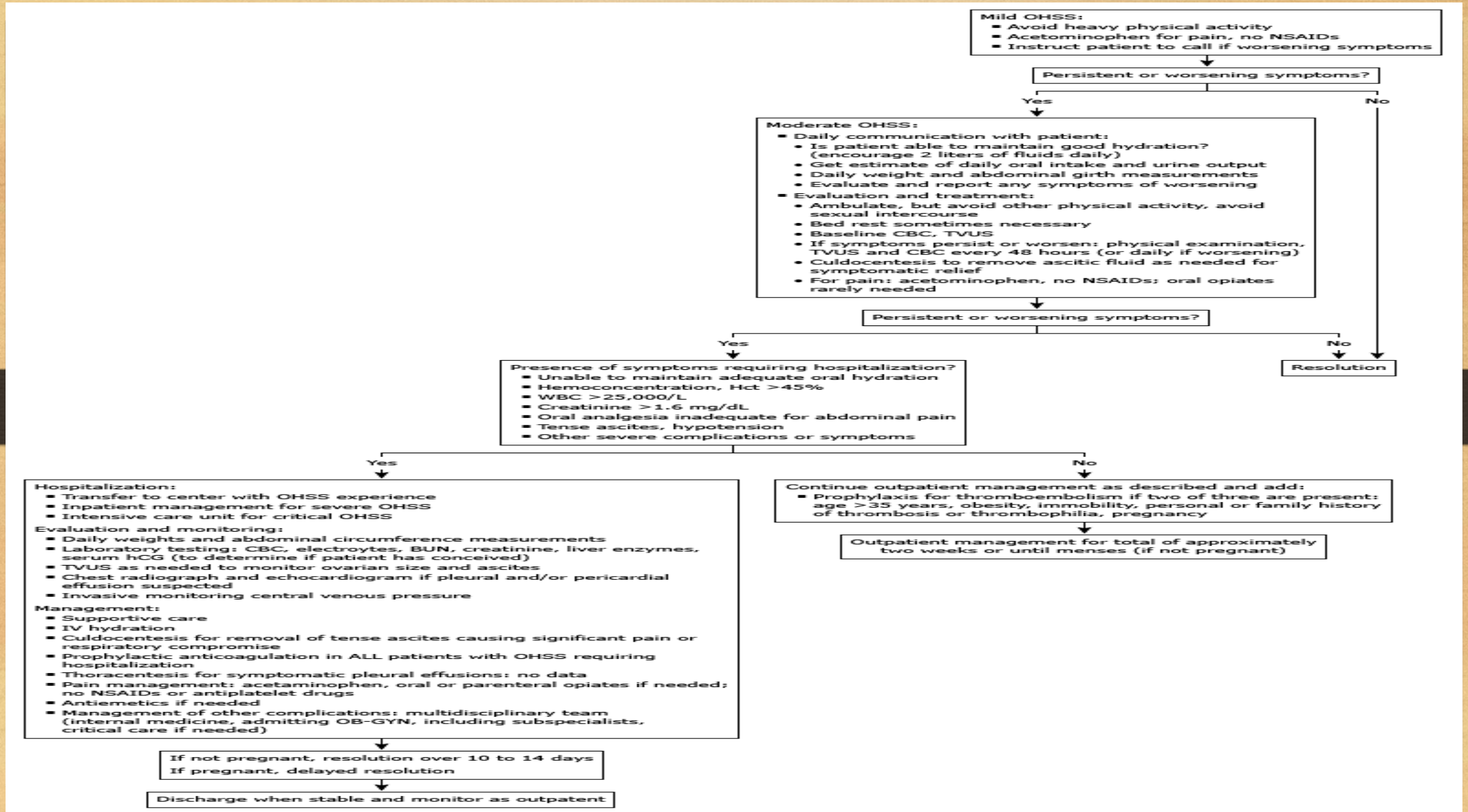
- It is not recommended to administer letrozole as an intervention to reduce rates of moderate-to-severe OHSS. (Strength of evidence: B; strength of recommendation: moderate).
- It is not recommended to administer a luteal GnRH antagonist alone to reduce rates of moderate-to-severe OHSS. Most studies report no reduction in rates of moderate-to-severe OHSS or signs or symptoms associated with OHSS. Some low-quality evidence suggests modest symptomatic improvement in women with OHSS who received a GnRH antagonist after the hCG trigger. (Strength of evidence: C; strength of recommendation: weak).

ASRM 2023

- It is not recommended to use aspirin as a primary strategy to reduce the incidence of OHSS. (Strength of evidence: C; strength of recommendation: weak).
- It is not recommended to administer metformin for the sole purpose of reducing the incidence of OHSS in GnRH antagonist cycles because most studies do not report a significant reduction in rates of OHSS in women with PCOS who were given metformin. Metformin may, however, be considered for OHSS risk reduction among women with PCOS using a GnRH-agonist protocol. (Strength of evidence: B; strength of recommendation: moderate).
- It is not recommended to administer medications such as mifepristone, myoinositol, D-chiro-inositol, or glucocorticoids to reduce rates of OHSS because studies have shown these interventions to be ineffective. (Strength of evidence: C; strength of recommendation: weak).

ASRM 2023

- It is recommended to consider a freeze-only cycle and subsequent frozen embryo transfer in patients at risk for OHSS on the basis of a high ovarian response or elevated serum estradiol levels. Multiple high-quality studies have reported a significant reduction in rates of moderate or severe OHSS when this strategy is employed. (Strength of evidence: A; strength of recommendation: strong).
- It is not recommended to use volume expanders such as albumin, hydroxyethyl starch, or mannitol in patients who are at high risk of developing moderate or severe OHSS. (Strength of evidence: C; strength of recommendation: weak).


Mild OHSS:
Avoid heavy physical activity
Acetominophen for pain, no NSAIDs
Instruct patient to call if worsening symptoms
Persistent or worsening symptoms?
Yes
No
Moderate OHSS:
Daily communication with patient:
Is patient able to maintain good hydration? (encourage 2 liters of fluids daily)
Get estimate of daily oral intake and urine output
Daily weight and abdominal girth measurements
Evaluate and report any symptoms of worsening
Evaluation and treatment:
Ambulate, but avoid other physical activity, avoid sexual intercourse
Bed rest sometimes necessary
Baseline CBC, TVUS
If symptoms persist or worsen: physical examination, TVUS and CBC every 48 hours (or daily if worsening)
Culdocentesis to remove ascitic fluid as needed for symptomatic relief
For pain: acetominophen, no NSAIDs; oral opiates rarely needed
Persistent or worsening symptoms?
Yes
No
Resolution
Presence of symptoms requiring hospitalization?
Unable to maintain adequate oral hydration
Hemoconcentration, Hct >45%
WBC >25,000/L
Creatinine >1.6 mg/dL
Oral analgesia inadequate for abdominal pain
Tense ascites, hypotension
Other severe complications or symptoms
Yes
No
Hospitalization:
Transfer to center with OHSS experience
Inpatient management for severe OHSS
Intensive care unit for critical OHSS
Evaluation and monitoring:
Daily weights and abdominal circumference measurements
Laboratory testing: CBC, electroytes, BUN, creatinine, liver enzymes, serum hCG (to determine if patient has conceived)
TVUS as needed to monitor ovarian size and ascites
Chest radiograph and echocardiogram if pleural and/or pericardial effusion suspected
Invasive monitoring central venous pressure
Management:
Supportive care
IV hydration
Culdocentesis for removal of tense ascites causing significant pain or respiratory compromise
Prophylactic anticoagulation in ALL patients with OHSS requiring hospitalization
Thoracentesis for symptomatic pleural effusions: no data
Pain management: acetaminophen, oral or parenteral opiates if needed; no NSAIDs or antiplatelet drugs
Antiemetics if needed
Management of other complications: multidisciplinary team (internal medicine, admitting OB-GYN, including subspecialists, critical care if needed)
If not pregnant, resolution over 10 to 14 days
If pregnant, delayed resolution
Discharge when stable and monitor as outpatent
Continue outpatient management as described and add:
Prophylaxis for thromboembolism if two of three are present: age >35 years, obesity, immobility, personal or family history of thrombosis or thrombophilia, pregnancy
Outpatient management for total of approximately two weeks or until menses (if not pregnant)

Thank You for Your Attention