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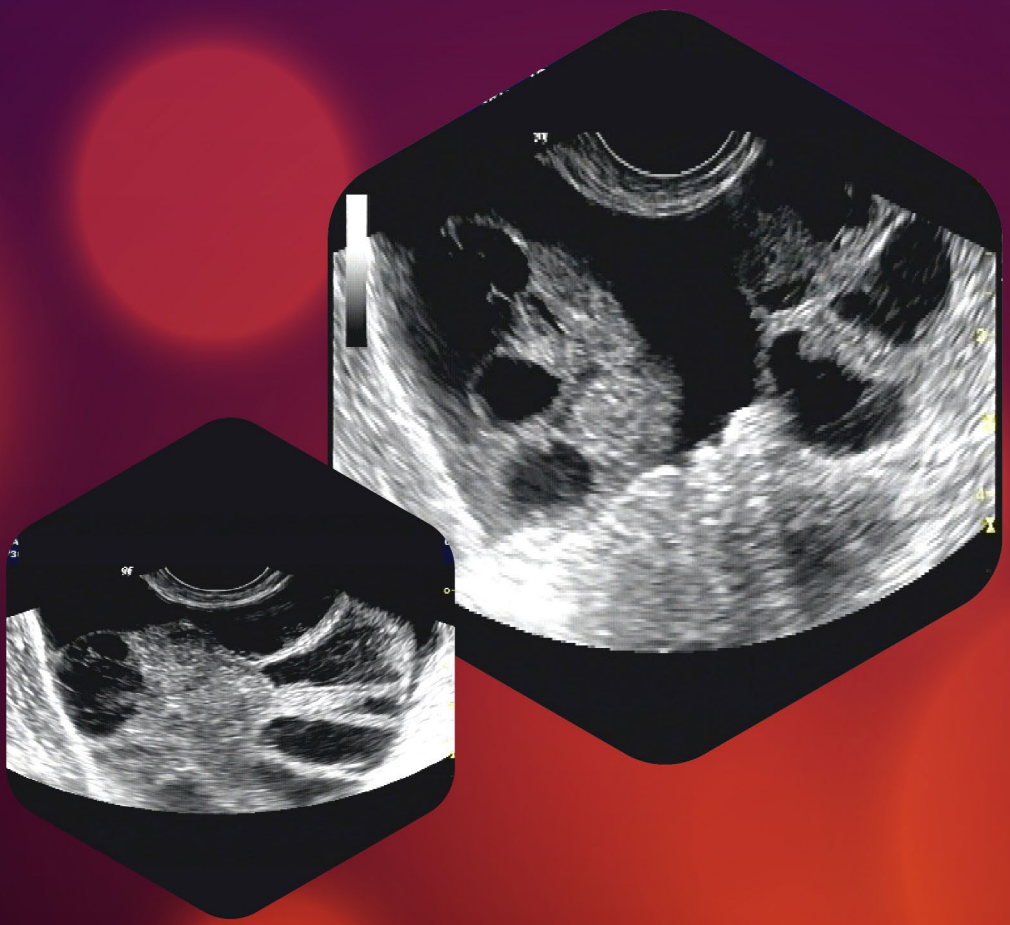
Ovarian Hyperstimulation Syndrome
The Complete Know - How



Chief Editor
Prof (Dr) Pankaj Talwar

Ovarian Hyperstimulation Syndrome The Complete Know - How

Dr M Gouri Devi
President - IFS

With great pride and honor, I write this message for the Eighth E-bulletin of IFS-ARTexT. ARText is our initiative to disseminate scientific and ethical (subject-related) knowledge, and to constantly update everyone with new researches and developments across the world. Through this endeavor, we aim to discuss and simplify the various complexities in clinical ART.

In the current issue, we will be discussing "Ovarian Hyperstimulation Syndrome" (OHSS). It is a potentially fatal complication of ovulation induction increasingly being recognised with the greater usage of various Assisted Reproductive Techniques. As the treatment of the syndrome is currently empirical, prevention is the most important aspect of its management and thus needs in depth discussion of its pathophysiology and various preventive measures.

I am sure that you would be benefited from this academic initiative of publication wing of IFS. Indian Fertility society feels proud and congratulates the editors for this bulletin.

Prof (Dr) Pankaj Talwar
Secretary General - IFS
Chief Editor - NEXUS & ARText

To start with, I would like to thank all the readers for appreciating and acknowledging the previous bulletins of ARTexT. Your encouragement motivates us to present more such bulletins in the field of the Assisted Reproductive Techniques. We have always believed in spreading awareness about the common issues in ART and tried to gather and present the evidence that will undoubtedly help both the clinicians and the patient.

In this bulletin we are going to dwell in detail "Ovarian Hyperstimulation Syndrome" a complication of ART which can progress from mild to critical OHSS if not timely recognized and intervened. OHSS is an iatrogenic disorder due to ovarian stimulation by gonadotropins resulting in ovarian enlargement and fluid shift from intravascular to extravascular compartment and multiple consequences which can prove to be fatal with a downhill course. This edition of ARText will highlight the pathophysiology, risk factors, clinical presentation and how prevention is of paramount importance in the treatment of OHSS.

I am sure that you would appreciate and learn from this academic initiative of IFS and will be able to apply the take home message in your busy daily clinical practice.

INVITED GUEST EDITOR

Dr Nikita Naredi
Director and Consultant
Assited Reproductive Medicine

Ovarian Hyperstimulation Syndrome is an iatrogenic complication due to an exaggerated response to exogenous gonadotropins in ART cycles and less commonly due to ovulation induction by clomiphene citrate. This syndrome although self limiting but if not timely recognised and intervened can have a downhill course and even prove to be fatal. With the pathophysiology still being enigmatic, the treatment is primarily symptomatic and thus prevention forms the mainstay of management.

This edition of ARText on OHSS aims to delve into the nuances of OHSS covering the various pathophysiological mechanisms implicated in its causation, identifying the risk factors and the various preventive measures which can be administered to achieve the dream of an "OHSS FREE CLINIC".

It is indeed a privilege to be given an opportunity to compile this topic which is very close to my heart and its prevention and elimination my aim.
Regards

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PART - 1
The Clinical Spectrum

1. Introduction

Ovarian hyperstimulation syndrome (OHSS), a potentially fatal complication of ovulation induction increasingly being recognised with the greater usage of various Assisted Reproductive Techniques remains a great challenge to fertility specialists. As the treatment of the syndrome is currently empirical, prevention is the most important aspect of its management and thus needs in depth discussion of its pathophysiology and various preventive measures.

2. Definition

Ovarian Hyperstimulation Syndrome (OHSS), an iatrogenic and a dreadful complication of controlled ovarian stimulation during Assisted Reproductive Technology (ART) occurs as an exaggerated response to exogenous gonadotropins and rarely to ovulation inducing agents like clomiphene citrate or due to spontaneous conception. This self limiting disorder characterised by various clinical manifestations due to increased capillary permeability and accumulation of fluid in the third space can have a downhill course and prove to be fatal if not timely recognised and intervened.

3. Incidence

The true incidence is difficult to delineate because of poor reporting and lack of strict consensus definition but moderate to severe OHSS occurs in approximately 1%-5% of cycles. Mild OHSS which occurs much more commonly i.e. in 20-30% of cycles has much less clinical relevance as compared to the moderate and severe ones.

4. History

The syndrome was first described in 1943 as **"syndrome d'hyperluteinisation massive des ovaries"** when early forms of gonadotropins (gonadotropic preparations from pregnant mare serum or urine from pregnant females) were used to stimulate or induce ovulation. It was in 1951 that the first fatal case of OHSS was reported occurring due to oliguric renal failure as the primary complication leading to mortality. In spite of its recognition for seven decades since its original description, OHSS continues to be a grave complication of ovarian stimulation.

5. Types

OHSS can be classified based on the severity of its presentation and the timing of its onset.

OHSS exists in a range of clinical spectrum ranging from mild signs and symptoms to moderate features and at the other extreme: severe and critical OHSS requiring intensive management which may even lead to fatality.

Depending on the time of onset, OHSS can be **early:** within 3-7 days of the exogenous hCG trigger, and the **late:** form: 9-12 days after hCG which is mainly related to the secretion of placental hCG i.e. endogenous hCG. . Late OHSS is more likely to be severe and prolonged than the early form.

6. Risk Factors

Identification of patients at risk is of critical importance during ovarian stimulation as OHSS is the most serious consequence of ART. Risk factor identification helps in instituting appropriate and timely preventive measures. The risk factors can be divided into:

Primary risk factors:

Patient characteristics or factors present before stimulation and likely to amplify the response to ovarian stimulation are primary risk factors. They include: young age, low BMI, a history of elevated response to gonadotrophins, previous OHSS, polycystic ovary syndrome (PCOS), a high serum anti Mullerian hormone level (AMH). Of all these AMH has gained greatest attention as proven by many workers. In a prospective cohort of 262 women undergoing IVF higher serum

antimullerian hormone levels (cut off >3.6ng/ml) predicted OHSS better than age and BMI with a sensitivity of 90.5%and specificity of 81.3%. In another study AMH levels were 6 fold higher than age and weight matched controls in patients with OHSS.

Lee TH, Liu CH, Huang CC,Wu YL, Shih YT,Ho HN,et al. Serum antimullerian hormone level andestradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproductive technology cycles. Hum reprod 2008; 23:160-7

Secondary risk factors:

Secondary risk factors are the ones which become obvious during the course of stimulation. These ovarian response parameters can be evaluated for their ability to predict the development of OHSS like: absolute levels or rate of increase of serum estradiol (E2), follicular size and number, and number of oocytes collected. Several prospective studies have demonstrated that greater number of growing follicles is an independent predictor of OHSS especially if 20 or more follicles are developed it significantly increases the risk.

Jayaprakasan K, Herbert M, Moody E, Stewart JA, Murdoch AP. Estimating the risks of ovarian hyperstimulation syndrome (OHSS): implications for egg donation for research. Hum Fertil (Camb). 2007; 10(3):183-7.

7. Etiopathogenesis

The exact etiopathological mechanism implicated for the causation of this syndrome is still elusive but the culprit molecule for its initiation has been documented to be human chorionic gonadotropin (hCG) as the syndrome does not develop if hCG is withheld. In addition various vasoactive substances have been suggested to perpetrate the pathophysiology of this disease including prorenin, rennin, prostaglandins, angiotensin II, vascular endothelial growth factor (VEGF), interleukins1β, 2,6 and tumour necrosis factor α (TNF). Of all these, it is VEGF also known as the 'vascular permeability factor' which has been found to play the most critical role. hCG per se, has no vasoactive property but the angiogenic molecule, VEGF is the important mediator of hCG-dependent ovarian angiogenesis. VEGF is expressed in human ovaries and it has been observed that VEGF mRNA levels increases after hCG administration in granulosa cells and VEGF levels correlate with OHSS severity. The other aforementioned vasoactive substances also act in concert directly or indirectly with VEGF to establish the pathogenesis of this iatrogenic complication. Thus all the preventive and treatment measures developed or being researched is targeted against VEGF.

The hallmark mechanism postulated for the presentation of this syndrome is increased vascular permeability and extravasation of fluid from the intravascular compartment to the third space compartment which in turn causes hemoconcentration with reduced organ perfusion, alterations in blood coagulation and leakage of fluid into the peritoneal cavity and lungs.[**Fig 1**] Factors which bring about these are:

- increased secretion or exudation of protein rich fluid from enlarged ovaries or peritoneal surfaces
- increased follicular fluid levels of prorenin and rennin
- angiotensin mediated changes in capillary permeability

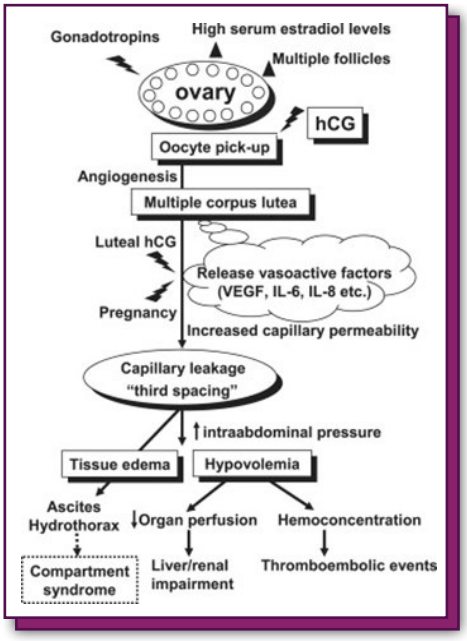


Fig 1: Pathophysiology of OHSS

8. Clinical Spectrum and classification of OHSS

Various classification systems have been put forth combining clinical, radiological and laboratory parameters but the clinical presentation is a continuous spectrum with overlap of one over the other. Based on the symptoms and associated features the disease process is qualified by its severity into mild, moderate, severe and critical.

Table: 1

OHSS Stage	Clinical Features	Laboratory Features
Mild	Abdominal distension/discomfort	No important alterations
	Mild nausea/vomiting	
	Mild dyspnoea	
	Diarrhoea	
	Enlarged ovaries	
Moderate	Mild features	Haemoconcentration(Hct>41%)
	Ultrasonographic evidence of ascites	Elevated WBC(>15,000 ml)
Severe	Mild and Moderate features	Severe Haemoconcentration(Hct>55%)
	Clinical evidence of ascites	WBC>25,000/ml
	Hydrothorax	Cr Cl<50ml/min
	Severe dyspnoea	Cr>1.6mg/dl
	Oliguria/anuria	Na^+<135mEq/L
	Intractable nausea/vomiting	K^+>5mEq/L Elevated Liver enzymes
Critical	Low blood/central venous pressure	Worsening of findings
	Pleural effusion	
	Rapid weight gain(>1 kg in 24 h)	
	Syncope	
	Severe abdominal pain	

Critical	Venous thrombosis	
	Anuria/Acute renal failure	
	Arrythmia	
	Thromboembolism	
	Pericardial effusion	
	Massive hydrothorax	
	Arterial Thrombosis	
	Adult respiratory distress syndrome	
	Sepsis	

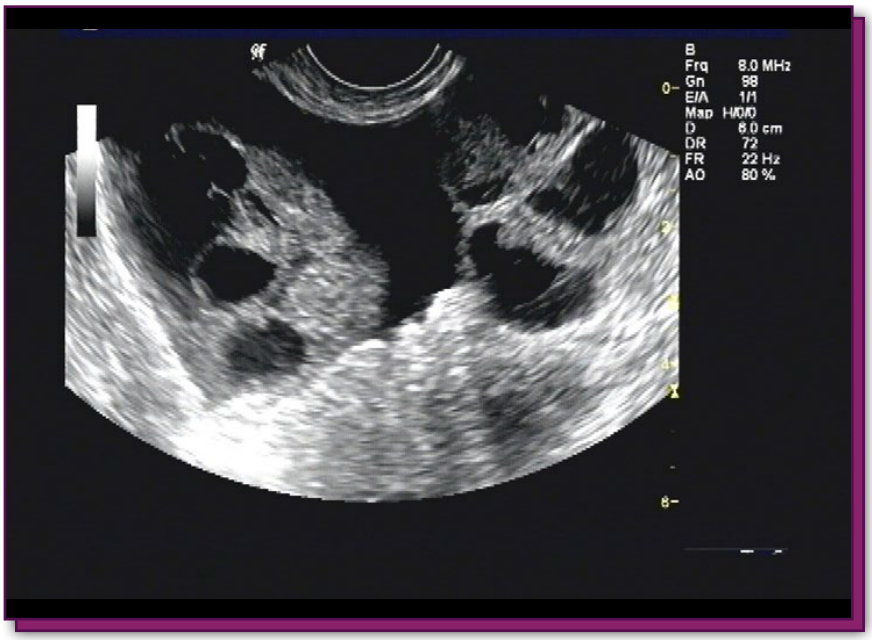


Fig 2: Ultrasonic evidence of Ascites

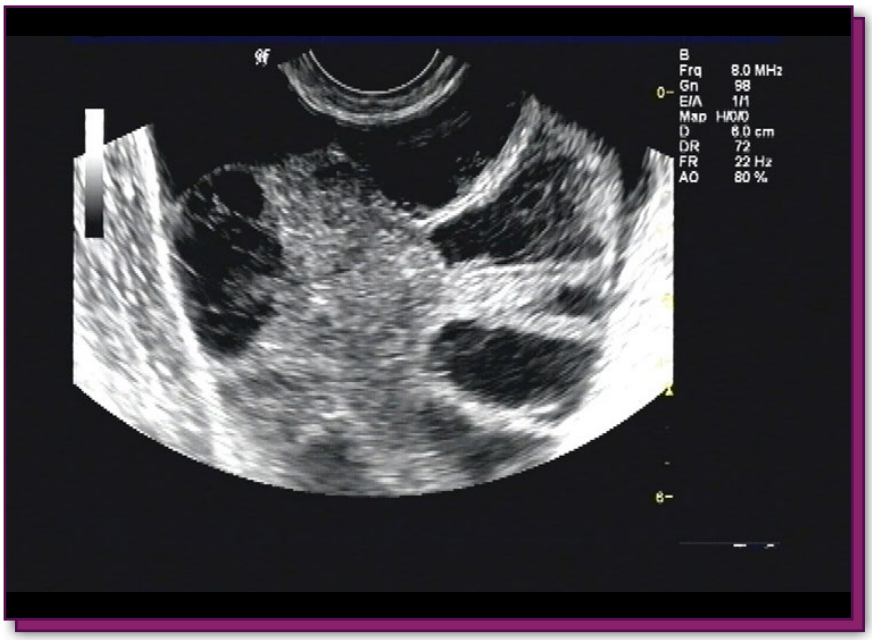


Fig 2: Ovarian enlargement on TVS

9. Prevention

Measures to treat and prevent OHSS have been intriguing fertility specialists for decades but no conclusive management protocol to eliminate it has been attained. The treatment has been primarily empirical and prevention has formed the mainstay of management. The preventive strategies aim, to target women at high risk and institution of various pharmacological and non pharmacological interventions on them. The various preventive strategies are:

i. Type of protocol

Multiple studies have demonstrated that stimulation protocols utilising gonadotropin releasing hormone (GnRH) antagonists for ovarian suppression are associated with a lower incidence of OHSS compared to GnRH agonist. The largest randomised study postulating this was a two centre, open labelled superiority trial of 1,050 patients comparing GnRH antagonist to GnRH agonist and the occurrence of OHSS. The incidence of severe OHSS was significantly lower in the antagonist group compared to the agonist group. These findings have been corroborated by multiple smaller RCTs.

Toftager M, Bogstad , Bryndorf T, Løssl K, Roskær J, Holland T, et al.Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. Hum Reprod. 2016 Jun;31(6):1253-64.

Ludwig M, Felberbaum RE, Devroey P, Albano C, Riethmüller-Winzen H, Schüler A, Engel W, Diedrich K. Significant reduction of the incidence of ovarian hyperstimulation syndrome (OHSS) by using the LHRH antagonist Cetrorelix (Cetrotide) in controlled ovarian stimulation for assisted reproduction. Arch Gynecol Obstet. 2000;264(1):29-32.

ii. Role of Aspirin

Increased platelet activation due to VEGF levels may lead to release of substances such as histamine, serotonin, platelet derived growth factor which can further potentiate the pathophysiological pathway of OHSS. Thus aspirin has been considered for reduction of OHSS. Two randomised trials on the use of aspirin 100mg from the day of stimulation until the day of pregnancy test have found a lower incidence of severe OHSS requiring hospital admission compared to women who were not on aspirin.

Várnagy A1, 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.

Revelli A1, Dolfin E, Gennarelli G, Lantieri T, Massobrio M, Holte JG, Tur-Kaspa . Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study. Fertil Steril. 2008; 90(5):1685-91.

iii. Metformin

Metformin an insulin sensitising drug has been widely studied for its role in PCOS patients. The hypotheses that androgens increase the response to gonadotropin stimulation by enhancing early follicular growth has been utilised for the usage of metformin. By improving intraovarian hyperandrogenism, metformin can affect the ovarian response by reducing the number of non periovulatory follicles and thereby reduces estradiol secretion. RCTs have shown that Metformin from the start of down regulation until oocyte retrieval in agonist protocols decreased the incidence of OHSS in PCOS women. A metanaalysis also revealed significant decrease in OHSS incidence with Metformin use.

Palomba S1, Falbo A, Carrillo L, Villani MT, et al. METformin in High Responder Italian Group. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertil

Steril. 2011 Dec;96(6):1384-1390.
Palomba S, Falbo A, La Sala GB. Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for in vitro fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials.BJOG 2013; 120(3): 267–276

iv. Coasting

Coasting which implies withholding gonadotropins at the end of COH for upto 4 days with an aim to reduce the risk of OHSS has also been postulated as a preventive strategy for OHSS. Although earlier studies found a role in lowering the risk of OHSS without compromising the pregnancy rate but they were not supported by RCTs. A systematic review of four RCTs concluded that coasting does not reduce the risk of OHSS but decreases the number of oocytes retrieved. Thus there is insufficient evidence to recommend coasting for prevention for OHSS.

Dhont M, Van der Straeten F, De Sutter P. Prevention of severe ovarian hyperstimulation by coasting. Fertil Steril 1998;70:847–50.

D'Angelo A1, Brown J, Amso NN. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2011; 15;(6):CD002811

v. Choice of trigger for final Oocyte maturation

hCG for final oocyte maturation prior to oocyte retrieval which mimics the endogenous preovulatory luteinising surge (LH) has been the norm for decades. However, the disadvantage with hCG is its longer half life which resulted in sustained LH like activity even after retrieval and further stimulation of LH receptors on the multiple corpora lutea and thus development of OHSS in at risk patients. A felt need was either alteration of the trigger dose or an alternative trigger as hCG is the culprit molecule. Studies were carried out if reducing the dose of hCG from 10,000IU to 5000IU would lower the risk of OHSS. An RCT evaluated 5,000IU vs 10000IUof hCG in high risk patients and reported a lower risk of OHSS in the low dose group but it did not reach statistical significance. Another RCT also did not find a difference in the OHSS rate in the two dosage group. In view of its doubtful role as a preventive modality another alternative was required.

GnRH agonist as a trigger has been studied extensively and has been seen to eliminate OHSS in an antagonist cycle. Several RCTS have proven its preventive role in OHSS development and especially in a high risk population like PCOS women. In a RCT which compared hCG with GnRH agonist, none of the women in the agonist trigger group developed OHSS.

Shaltout, A.M., Eid, M., Shohayeb, A. Does triggering ovulation by 5000 IU of uhCG .affects ICSI outcome? Middle East Fertil Soc J. 2006; 11:99–103

Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril. 2008; 89(1):84-91.

vi. Dopamine Agonist

As VEGF is the main vasoactive substance implicated in the pathophysiology of OHSS, it was postulated that VEGF antagonist in the form of a dopamine agonist may result in reduction of VEGF and thus the vascular permeability and other manifestations. There is a growing evidence that dopamine agonist in the form of Cabergoline has reduced both the severity and the incidence of OHSS. Cabergoline is administered in the dose of 0.5 mg/day for 8 days starting from the day of hCG trigger. A prospective randomised study assessed oocyte donors who were administered Cabergoline

or placebo from the day of hCG. The incidence of OHSS was much lesser in the Cabergoline group as compared to the placebo group. Other RCTS have also corroborated the same finding.

Tehraninejad ES, Hafezi M, Arabipoor A, Aziminekoo E, Chehrazi M, Bahmanabadi A. Comparison of cabergoline and intravenous albumin in the prevention of ovarian hyperstimulation syndrome: a randomized clinical trial. J Assist Reprod Genet. 2012; 29(3):259-64.

Alvarez C1, Martí-Bonmatí L, Novella-Maestre E, Sanz R, Gómez R, Fernández-Sánchez M, Simón C, Pellicer A. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab. 2007; 92(8):2931-7.

vii. Albumin

Albumin because of its inherent property of binding proteins increases the plasma oncotic pressure and counteracts the permeability of angiotensin II and thus may play a role in the prevention of OHSS. However data on its efficacy as a preventive strategy are mixed with some studies demonstrating reduction in the incidence of moderate-severe OHSS by administering 20% human albumin around the time of oocyte rereival while some researchers have not found to be effective in a preventive role. Two systematic reviews have also concluded that intravenous albumin administration in high-risk patients does not appear to reduce the occurrence of severe OHSS.

Isik AZ, Gokmen O, Zeyneloglu HB, Kara S, Keles G, Gulekli B. Intravenous albumin prevents moderate-severe ovarian hyperstimulation in in-vitro fertilization patients: A prospective, randomized and controlled study. Eur J Obstet Gynecol Reprod Biol. 1996; 70:179–83

Venetis CA, Kolibianakis EM, Toulis KA, Goulis DG, Papadimas I, Basil C. Tarlatzis BC. Intravenous albumin administration for the prevention of severe ovarian hyperstimulation syndrome: a systematic review and metaanalysis. Fertil Steril 2011;95(1) : 188–196

viii. Calcium Gluconate Infusion : A new tool

Increased calcium has been found to inhibit cAMP stimulated rennin secretion which decreases angiotensin II synthesis and finally prevents VEGF release breaking the pathway for OHSS occurrence. With this background studies have investigated the usage of calcium gluconate infusion 10ml of 10% calcium gluconate in 200ml normal saline on day of ovum pick up and days 1,2 and 3 thereafter. The incidence of moderate –severe OHSS was lesser in the calcium group in an RCT comparing calcium versus normal saline in a high risk group. Another case control study revealed that IV calcium is as effective as Cabergoline in preventing severe OHSS

El-Khayat et al.Calcium infusion for the prevention of ovarian hyperstimulation syndrome: A double-blind randomized controlled trial. Fertil Steril 2015; 103: 101–5
Naredi N, Karunakaran S. Calcium gluconate infusion is as effective as the vascular endothelial growth factor antagonist cabergoline for the prevention of ovarian hyperstimulation syndrome. JHRS 2013;6(4):248-252

ix. Cryopreservation of embryos

A 'freeze all' technique or elective cryopreservation of all the embryos with an aim to transfer in the subsequent non stimulated cycles is adopted to prevent the endogenous hCG rise should a pregnancy happen and further exacerbate the late onset OHSS symptoms and increase the severity and duration. Two RCTS have demonstrated that elective cryopreservation prevents OHSS. With better vitrification techniques and better pregnancy rates in a frozen cycle elective cryopreservation is a viable and preferred modality to prevent late onset OHSS.

Sills ES, McLoughlin LJ, Genton MG, Walsh DJ, Coull GD, Walsh AP. Ovarian hyperstimulation syndrome and prophylactic human embryo cryopreservation: analysis of reproductive outcome following thawed embryo transfer. J Ovarian Res. 2008; 1: 7

Chen H1, Wang B, Xu ZP, Sun HXClinical outcomes of fresh versus cryopreserved-thawed embryo transfer in high-risk patients with ovarian hyperstimulation syndrome. Zhonghua Nan Ke Xue. 2014; 20(11):1008-11

x. Luteal Phase Antagonist

GnRH antagonist was found to lower the VEGF concentrations in human granulosa lutein cell cultures as well as the expression of VEGF and VEGF-R in the ovaries of hyper stimulated rats. Due to its prominent luteolytic effect it might prove to be an alternative way of reducing the excessive production of vasoactive cytokines from the corpora lutea responsible for OHSS development. This background has led to the use of reinitiation of GnRH antagonist in the luteal phase after oocyte retrieval for the prevention of severe early OHSS.

Lainas et al were the first to investigate the use of antagonist in the luteal phase in patients at risk for OHSS. They

started luteal GnRH antagonist and fresh blastocyst transfer in three patients with early-stage OHSS. In all their patients, severe OHSS regressed to a moderate form and no pregnancy-induced severe OHSS was observed. In another observational study luteal phase antagonist was a made a part of the multipronged approach in preventing severe OHSS. The luteolytic effect of the GnRH antagonist has been proposed as the main theory to explain the mode of action of this drug to prevent OHSS. Further larger studies are required to establish its preventive role.

Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Kolibianakis EM. Management of severe early ovarian hyperstimulation syndrome by re-initiation of GnRH antagonist. Reprod Biomed Online. 2007;15(4):408–12.

Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Iliadis GS, et al. Management of severe OHSS using GnRH antagonist and blastocyst cryopreservation in PCOS patients treated with long protocol. Reprod Biomed Online. 2009;18(1):15–20.

Naredi N, Singh SK, Lele P , Nagraj N Severe ovarian hyperstimulation syndrome: Can we eliminate it through a multipronged approach? MJAFI 2018;74(1):44-50

10. Innovative Strategies

i. In Vitro Maturation

In vitro maturation with IVF (IVM) is a modality for avoiding any degree of OHSS since oocytes are harvested from medium to large antral follicles before in vivo follicle selection begins. With IVM, immature oocytes complete meiosis II over the next 48 h and are then fertilized once they become mature. IVM may be advocated as "rescue IVM" as it may prevent severe OHSS in the setting of conventional IVF. "Rescue IVM" means that the physician has concluded that a conventional IVF cycle can not safely proceed and the physician changes the treatment direction by immediately applying that program's IVM protocol to the cycle. If aspiration occurred before follicle selection takes place, then the risk of OHSS was eliminated.

Inspite of its advocated theoretical benefit for prevention of OHSS In vitro maturation should only be performed as an experimental procedure in specialized centers for carefully selected patients evaluating both efficacy and safety.

ii. Kisspeptin

Kisspeptins are a family of neuropeptides of varying length encoded by the KISS1 gene. The most abundant isoform of kisspeptin in the human circulation is kisspeptin-54. It has been found that kisspeptin is a critical regulator of the reproductive axis by stimulating endogenous GnRH secretion from hypothalamic neurones. Studies have demonstrated that peripheral administration of kisspeptin-54 led to a maximal LH response during the preovulatory phase of the menstrual cycle, suggesting that kisspeptin is responsible for the mid-cyclical LH surge, and can thus be used as a trigger of oocyte maturation in a GnRH antagonist protocol instead of hCG during an IVF cycle.
In a pilot study it was observed that when increasing doses of a single subcutaneous kisspeptin-54 injection to act as a trigger in a GnRH antagonist protocol following superovulation with FSH was used, kisspeptin-54 dose-dependently increased the number of mature oocytes per patient, with the transfer of resulting embryos leading to clinical pregnancy. In a subsequent trial investigating the safety and efficacy of a kisspeptin trigger in women at high risk of OHSS, with either a serum AMH level of >40 pmol/L or an antral follicle count of >23, none of the women developed moderate, severe or critical OHSS following embryo transfer. Nevertheless such promising results need further clarification from larger RCTs of women at risk of developing OHSS comparing kisspeptin with existing therapies for egg maturation during to form an evidence base for this novel treatment. Early trials have produced encouraging results, but this area of research is still very much in its infancy.

Dhillo WS, Chaudhri OB, Thompson EL, et al. Kisspeptin-54 stimulates gonadotropin release most potently during the preovulatory phase of the menstrual cycle in women. J Clin Endocrinol Metab 2007; 92(10): 3958–3966.

Jayasena CN, Abbara A, Comninos AN, et al. Kisspeptin-54 triggers egg maturation in women undergoing in vitro fertilization. J Clin Invest 2014; 124(8): 3667–3677

11. Treatment of OHSS

In spite of preventive measures if OHSS does occur then treatment is primarily symptomatic and the main principle for treatment is fluid replacement to maintain intravascular perfusion and supportive care to prevent further complications. Treatment modalities to revert the pathophysiological cycle which has already set in are still investigational and thus treatment is empirical. Multidisciplinary assistance should be sought for the care of women with critical OHSS and severe OHSS who have persistent haemoconcentration and dehydration. Features of critical OHSS should prompt consideration of the need for intensive care. .A clinician experienced in the management of OHSS should remain in overall charge of the woman's care.

i. Fluid management

Fluid replacement by the oral route, guided by thirst, is the most physiological approach to correcting intravascular dehydration. Women with persistent haemoconcentration despite volume replacement with intravenous colloids may need invasive monitoring and this should be managed with the help of an intensivist. 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.

12. Paracentesis / Culdocentesis

An important treatment modality once severe OHSS has set in is: paracentesis as the third space shift in the form of increased ascitic fluid accumulation leads to an abdominal compartment syndrome with multiple manifestations.
Indications for paracentesis include the following:

- severe abdominal distension and abdominal pain secondary to ascites
- shortness of breath and respiratory compromise secondary to ascites and increased intra-abdominal pressure
- oliguria despite adequate volume replacement,

i. Outpatient vs inpatient

In view of the fear for vascular or ovarian injury with paracentesis, there were reservations for it being done in an outpatient setting. Studies have proven that using ultrasound guidance the chances are very rare.
A study has demonstrated that women with OHSS and ascites managed with repeated transvaginal ascetic fluid aspiration and rehydration with IV crystalloids and albumin every 1-3 days brought about resolution of the signs and symptoms. Another research on culdocentesis for severe OHSS found it to be associated with better recovery compared to the control group who were managed conservatively.

Lincoln SR, Opsahl MS, Blauer KL, Black SH, Schulman JD. Aggressive outpatient treatment of ovarian hyperstimulation syndrome with ascites using transvaginal culdocentesis and intravenous albumin minimizes hospitalization. J Assist Reprod Genet. 2002;19:159–163
Casals G1, Fábregues F, Pavesi M, Arroyo V, Balasch J.Conservative medical treatment of ovarian hyperstimulation syndrome: a single center series and cost analysis study. Acta Obstet Gynecol Scand. 2013 Jun;92(6):686-91.

ii. Surgical Management

The only indication of surgery in OHSS is when there is a suspected ovarian torsion or haemorrhage secondary to follicular rupture. Worsening pain, further ovarian enlargement,nausea, leucocytosis and anemia can raise the doubt of torsion which may be confirmed by a colour doppler analysis of the ovarian blood flow. Surgery should be conservative with minimal ovarian manipulation and to be performed by a senior person as the ovaries are highly vascular and friable.

PART - 2
Frequently Asked Questions

Q 1 Which patients with OHSS are suitable for outpatient care?

Outpatient management is appropriate for women with mild or moderate OHSS and in selected cases with severe OHSS. Women undergoing outpatient management of OHSS should be appropriately counselled and provided with information regarding fluid intake and output monitoring and the signs and symptoms of progressing illness. In fact in a study by Lianas et al they found for the first time, that successful outpatient management of severe OHSS with antagonist treatment in the luteal phase is feasible and is associated with rapid regression of the syndrome, challenging the dogma of inpatient management.

Recommendations for the outpatient management of persistent and worsening OHSS include:

- Oral fluid intake should be maintained at no less than 1 L per day;.
- Strenuous physical activity should be avoided as risk of ovarian torsion increases when the ovaries are significantly enlarged.
  Light physical activity should be maintained to the extent possible.
  Strict bed rest is unwarranted and may increase risk of thromboembolism.
- Weight should be recorded daily, as well as the frequency and/or volume of urine output.
- Pregnant patients with OHSS must be monitored very closely because risk of progressing to severe disease is particularly high for those further stimulated by rapidly rising serum concentrations of hCG.

Lainas GT, Kolibianakis EF, Sfontouris L A, Zorzovilis L Z, Petsas G K, Tarlatzi T B, et al. Outpatient management of severe early OHSS by administration of GnRH antagonist in the luteal phase: an observational cohort study. Reprod Biol Endocrinol. 2012; 10: 69.

Ovarian hyperstimulation syndromeThe Practice Committee of the American Society for Reproductive Medicine. November 2008Volume 90, Issue 5, Supplement, Pages S188–S193

Q 2 When should women with OHSS be admitted?

Hospital admission should be considered for women who:

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

The Management of Ovarian Hyperstimulation Syndrome RCOG Green-top Guideline No. 5; February 2016

Q 3 What is the role of thromboprophylaxis in OHSS?

The most serious complication associated with OHSS is a thrombotic phenomenon. To address the hypercoagulable state of OHSS anticoagulation or prophylactic thromboprophylaxis may be required. Patients diagnosed with OHSS and who need hospitalization, history of thrombophillias or any intervention should be started on thromboprophylaxis immediately. Thromboprophylaxis should be continued until resolution of OHSS or at least until week 12+6 in pregnancy or thereafter if additional risk factors are there. Thromboprophylaxis can be discontinued 4 weeks after resolution of OHSS in patients who are not pregnant.

CONCLUSION

OHSS, the most severe complication of ovarian stimulation with a potential to prove fatal if not timely intervened needs a risk acknowledgement even before the beginning of an IVF cycle. Although the exact etiolopathology remains elusive various implicating molecules have been studied which can be targeted before its occurrence; thus prevention remains the mainstay of management. Identifying the patients at risk, individualisation of the stimulation protocol, agonist trigger, targeting the causative molecules with various preventive modalities, close monitoring and adopting a 'freeze all strategy' can make the dream of **'OHSS free clinic'** a reality .

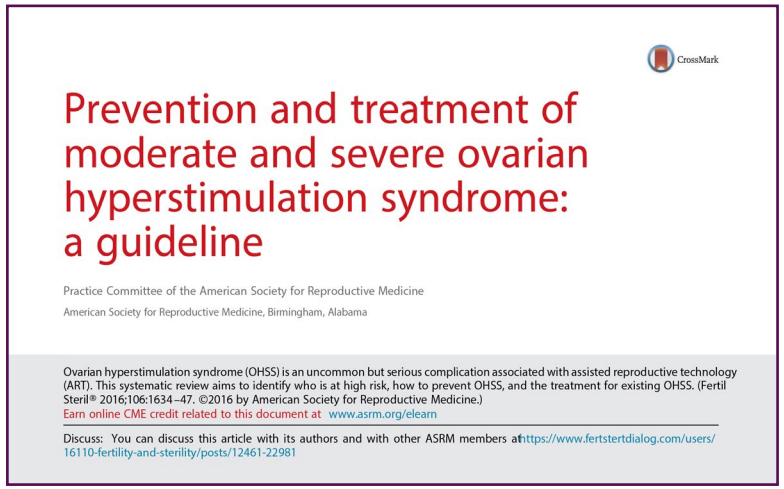
PART - 3

Review of International guidelines pertaining to Ovarian Hyperstimulation Syndrome

Adapted from ASRM and RCOG Guidelines

1 Recommended guidelines for OHSS

i. Prevention and treament of moderate and severe OHSS a guideline



Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Ovarian hyperstimulation syndrome (OHSS) is an uncommon but serious complication associated with assisted reproductive technology (ART). This systematic review aims to identify who is at high risk, how to prevent OHSS, and the treatment for existing OHSS. (Fertil Steril® 2016;106:1634–47. ©2016 by American Society for Reproductive Medicine.)

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The quality of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence. The strength of the evidence was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Classification of OHSS symptoms

OHSS Stage	Clinical Feature	Laboratory Feature
Mild	Abdominal distension/discomfort No important alterations Mild nausea/vomiting Mild dyspnea Diarrhea	Enlarged ovaries
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 Creatinine clearance (CrCl) <50 mL/min Creatinine (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

Summary Statements

S. No.	Summary Statements	Grade of Recommendation
1.	There is fair evidence (level II-2) that PCOS, elevated AMH values, peak estradiol levels, multi-follicular development, and a high number of oocytes retrieved increase the risk of OHSS.	Grade B
2.	While cut points require validation, AMH values >3.4 ng/mL, AFC >24, development of R25 follicles, estradiol values >3,500 pg/mL, orR24 oocytes retrieved are particularly associated with an increased risk of OHSS.	Grade B
3.	There is good evidence to support the use of ovarian stimulation protocols using GnRH antagonists in order to reduce the risk of OHSS.	Grade A
4.	There is insufficient evidence that clomiphene independently reduces OHSS risk.	Grade C
5.	There is fair evidence that aspirin reduces the incidence of OHSS based on a single, randomized trial comparing aspirin alone with no treatment and another study comparing combined acetylsalicylic acid and steroid treatment with no treatment.	Grade B
6.	There is good evidence that metformin decreases the risk of OHSS risk in PCOS patients.	Grade A
7.	There is insufficient evidence to recommend coasting for the prevention of OHSS.	Grade C
8.	There is insufficient evidence to recommend a lower dose of hCG to trigger oocyte maturation for reduction in OHSS risk based on one underpowered randomized trial.	Grade C
9.	There is good evidence to recommend the use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval in order to reduce the risk of OHSS.	Grade A
10.	There is good evidence that live-birth rates are lower in fresh autologous cycles after GnRH trigger, but not donor-recipient cycles.	Grade A
11.	There is fair evidence that reproductive outcomes are improved when a low dose of hCG is co administered at the time of GnRH agonist trigger for luteal support.	Grade B
12.	There is good evidence that dopamine agonist administration starting at the time of hCG trigger for several days reduces the incidence of OHSS.	Grade A
13.	There is insufficient evidence to conclusively state that albumin lowers OHSS risk.	Grade C
14.	There is fair evidence that calcium lowers OHSS risk.	Grade B
15.	There is fair evidence that cryopreservation prevents OHSS, based on the results of two small RCTs.	Grade B
16.	There is fair evidence to recommend paracentesis or culdocentesis for the management of OHSS in an outpatient setting.	Grade B
17.	There is insufficient evidence to support the use of volume expanders alone in treatment of OHSS.	Grade C

S. No.	Recommendations	Grade of Recommendation
1.	Women with PCOS, elevated AMH values, and elevated AFC may benefit from ovarian stimulation protocols that reduce the risk of OHSS.	Grade B
2.	Ovarian stimulation protocols using GnRH antagonists are preferable in women at high risk of OHSS.	Grade A
3.	The use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval is recommended to reduce the risk of OHSS if peak estradiol levels are high or multi-follicular development occurs during stimulation.	Grade A
	Low-dose hCG co-trigger, luteal hormonal support, or cryopreservation of embryos are strategies that may improve pregnancy rates in this setting.	Grade B
4.	Dopamine agonist administration starting at the time of hCG trigger for several days also may be used to reduce the incidence of OHSS.	Grade A
5.	Additional strategies to prevent OHSS which may be helpful include the use of : Metformin in PCOS patients	Grade A
	Aspirin administration	Grade A
	Cryopreservation of embryos	Grade B
6.	The mainstay of OHSS treatment includes fluid resuscitation and prophylactic anticoagulation. Paracentesis or culdocentesis may be recommended for management of OHSS when a large amount of ascites is present.	Grade B

ii. The management of OHSS

Article	Classification of evidence levels		Grades of recommendations	
	1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	**A**	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting princi-pally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
	1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	**B**	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
	1-	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	**C**	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
	2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–co trol or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	**D**	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
	2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	**GPP**	Recommended best practice based on the clinical experience of the guideline development group
	2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal		
	3	Non-analytical studies, e.g. case r ports, case series		

Executive summary of recommendations:

Summary	Recommended Good Practice Points (GPP)
How should OHSS be reported?	Licensed centers should comply with Human Fertilization and Embryology Authority (HFEA) regulations in reporting cases of severe or critical OHSS among their patients.
	Units that treat women with OHSS should inform the licensed centre where the fertility treatment was carried out to promote clinical continuity and to allow the licensed centre to meet its legal obligations.
How should care be delivered for women at risk of OHSS?	All acute units where women with suspected OHSS are likely to present should establish agreed local protocols for the assessment and management of these women and ensure they have access to appropriately skilled clinicians with experience in the management of this condition.
	Licensed centres that provide fertility treatment should ensure close liaison and coordination with acute units where their patients may present.
How should women with OHSS managed on an outpatient basis be monitored?	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.
Who should provide care to women with OHSS?	A clinician experienced in the management of OHSS should remain in overall charge of the woman's care.
What is the appropriate management of fluid balance?	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.
How should the risk of thrombosis be managed?	Women with moderate OHSS should be evaluated for predisposing risk factors for thrombosis and prescribed either antiembolism stockings or LMWH if indicated.

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RECOMMENDATIONS

- More research is required to clarify changes in the osmoregulatory system in women at different phases of OHSS, using well-defined cohorts of women with severe disease who are followed through the course of the OHSS.
- There is a need to compare outpatient and inpatient management of severe OHSS in terms of safety, efficacy, patient acceptability and health economic assessment. Such a trial could compare a 'conventional' approach of inpatient management with conservative indications for abdominal paracentesis with a more 'active' approach emphasising earlier paracentesis on an outpatient basis.
- Further research is required to evaluate the role of GnRH antagonists and dopamine agonists in the management of women with established OHSS.

Notes

Notes

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