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Review

Iatrogenic Ovarian Hyperstimulation Syndrome: Current Insights in to Therapeutic Advances

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Abstract

Ovarian Hyperstimulation Syndrome (OHSS) is an iatrogenic complication that arises due to an exaggerated ovarian response to exogenous gonadotropin administration, particularly during assisted reproductive techniques such as *in vitro* fertilization. Although most commonly associated with injectable gonadotropins, OHSS may also occur, albeit less frequently, with agents like clomiphene citrate or gonadotropin-releasing hormone analogues. Clinically, this manifests as abdominal distension, bloating, nausea, and ascites. In more severe presentations, patients may experience thromboembolic events, dyspnea due to pleural effusion, severe abdominal pain, hemoconcentration, dehydration, and intractable vomiting. A hallmark of OHSS is bilateral ovarian enlargement, with the degree of enlargement correlating with the severity of the syndrome. This review aims to explore the current evidence surrounding effective strategies for the prevention of ovarian hyperstimulation syndrome. Although a definitive method to completely eliminate the risk of OHSS has not yet been established, significant progress has been made by tailoring treatment protocols according to a patient's individual risk profile. Stratifying women based on their susceptibility to OHSS has shown promise, particularly through the use of biomarkers such as Anti-Müllerian Hormone (AMH) levels and antral follicle count (AFC), which help predict ovarian response. Early identification and stratification of OHSS severity are critical in guiding management decisions, ranging from outpatient surveillance to inpatient care for moderate-to-critical cases.

Keywords: Ovarian Hyperstimulation Syndrome, prophylactic antibiotic, clinical biomarkers, gonadotropin-releasing hormone, assisted reproductive technology.

INTRODUCTION

Ovarian Hyperstimulation Syndrome (OHSS) is a potentially life-threatening, iatrogenic complication that occurs primarily during Controlled Ovarian Stimulation (COS) in assisted reproductive technologies (ART). COS is employed to stimulate multifollicular development in the ovaries to enhance oocyte yield during procedures such as *in vitro* fertilization (IVF). While COS is central to the success of ART, it carries the risk of excessive ovarian response in certain individuals, leading to OHSS. OHSS is primarily associated with the use of exogenous gonadotropins and the administration of human chorionic gonadotropin (hCG) to trigger ovulation. Although the majority of OHSS cases are iatrogenic, spontaneous forms have also been documented, particularly in patients undergoing ovulation induction with clomiphene citrate or GnRH agonists. This review discusses the current understanding of OHSS pathophysiology and outlines recent therapeutic strategies developed to prevent and manage this condition effectively [1,2].

Infertility has emerged as a significant global health concern, affecting millions of couples and steadily increasing in prevalence. Assisted reproductive technologies (ART) have become a cornerstone in the management of infertility, offering renewed hope for many. While ART procedures are generally considered safe and effective, they are not without risks. One of the most serious iatrogenic complications associated with ovarian stimulation in ART is ovarian hyperstimulation syndrome (OHSS). OHSS results from an exaggerated ovarian response to stimulation and is closely linked to elevated levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), and estradiol (E2). The pathophysiology of OHSS is multifactorial. It involves the leakage of protein-rich fluid into the third space from the ovaries and peritoneal surfaces, an increase in follicular fluid concentrations of prorenin and renin, and alterations in vascular permeability, likely mediated by angiotensin and other vasoactive substances.

In some rare cases, spontaneous OHSS may occur due to genetic mutations affecting FSH or LH/hCG receptors, which highlight the central role of gonadotropins in the development of this condition. OHSS is categorized into different clinical grades: mild, moderate, severe, and critical, with the mild form being the most commonly observed [3-7].

This review aims to consolidate the current scientific understanding of OHSS by exploring its etiology, pathophysiology, and therapeutic approaches. Additionally, it emphasizes the importance of evidence-based prevention and management strategies. As in-depth appreciation of these aspects is crucial not only for effective clinical care but also for safeguarding against potential medico logical consequences in cases of adverse outcomes.

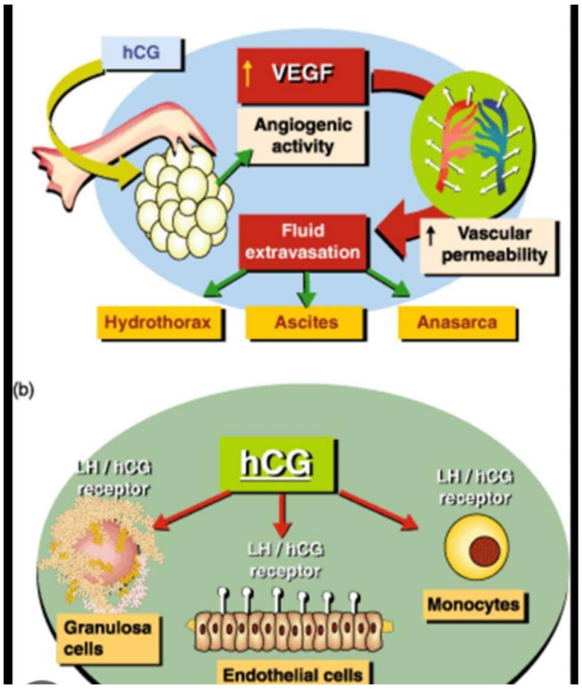

Fig 1: This diagram illustrates the pathophysiology of OHSS, highlighting how hCG stimulates VEGF production via LH/hCG receptors on granulosa, endothelial cells, and monocytes. The resulting increase in vascular permeability leads to fluid extravasation, causing ascites, hydrothorax, and anasarca Pathophysiology

The central mechanism of OHSS involves a marked increase in capillary permeability, which causes fluid to shift from the vascular compartment into third spaces such as the abdominal or pleural cavity. A key mediator of this vascular response is vascular endothelial growth factor (VEGF), which is secreted by granulosa cells and stimulated by hCG administration. Elevated VEGF levels correlate with the severity of OHSS.

Additional molecular contributors include a wide range of cytokines and growth factors-such as interleukin-6, interleukin-1β, transforming growth factors (TGF-α and TGF-β), platelet-derived growth factor, and insulin-like growth factors-which may amplify the vascular and inflammatory response. The renin-angiotensin system (RAS), particularly its intra-ovarian activity, is also implicated. Evidence shows that hCG activates this system, leading to increased renin concentrations in follicular fluid, further intensifying vascular changes and fluid leakage [8-11].

Prevention

Since complete elimination of OHSS risk is currently not feasible, prevention remains the most effective and preferred strategy. Prevention depends largely on early identification of at-risk patients and tailored clinical approaches [12-14].

Risk factors

- Primary Risk Factors: These include young age, low body mass index (BMI), polycystic ovarian syndrome (PCOS), and a history of previous OHSS episodes.
- Biomarkers for Prediction: Elevated serum anti-Müllerian hormone (AMH) levels (>3.36 ng/mL) and antral follicle count (AFC) ≥24 indicated heightened ovarian response.
- Ovarian Response Indicators: Monitoring during controlled ovarian stimulation (COS) reveals risk based on a high number of follicles (>14) and a steep rise in serum estradiol levels (>2500 pg/mL) [15-17].

Primary prevention strategies

- Customized Ovulation Induction Protocols: Individual risk assessments should guide drug selection and dosing. Patients with PCOS, for example, benefit from "step-up" gonadotropin protocols starting at low doses (e.g., 75 IU), with gradual increases only if the ovarian response is inadequate.
- Metformin Use: Metformin, particularly in PCOS patients, has been shown to reduce OHSS incidence significantly. A daily dose between 1000–2000 mg for at least 2 months before COS is recommended.
- Aromatase Inhibitors: These reduce estrogen synthesis and preserve feedback mechanisms that prevent overstimulation. However, recent reviews show no significant advantage in reducing OHSS over other induction agents.
- Tailored IVF Protocols: Adjusting COS protocols using AMH and AFC data ensures safer stimulation. Personalizing gonadotropin doses can reduce the risk of excessive follicular response.
- Laparoscopic Ovarian Drilling (LOD): For PCOS patients, LOD offers an alternative approach before stimulation. It helps reduce gonadotropin requirements and may induce spontaneous ovulation. Optimal results are seen in lean women with elevated LH levels when 4–10 punctures per ovary are made.

Alternative Ovulation Triggers

- Modified hCG Triggering: Using reduced doses of hCG (e.g., 5000 IU or less) may help decrease OHSS risk, especially when estradiol levels are high. However, consensus is lacking on dose reductions alone as a preventive measure.
- GnRH Agonist (GnRHa) Triggering: In antagonist-based IVF cycles, using a GnRH agonist instead of hCG to trigger ovulation can drastically reduce the risk of OHSS. Though associated with lower pregnancy rates unless combined with luteal support or freeze-all strategies, this method is a key part of OHSS-free protocols.
- Recombinant LH: While theoretically beneficial due to its shorter half-life compared to hCG, studies have shown no significant benefit in reducing OHSS. Additionally, recombinant LH is costlier and may lower pregnancy rates.

Stimulation Protocol Choice

- GnRH Antagonist Protocols: Compared to traditional long agonist protocols, GnRH antagonist cycles offer a significantly reduced OHSS risk in high-risk women. While earlier concerns existed about reduced success rates, recent evidence supports their efficacy and safety [18-23].

Treatment

The clinical treatment of OHSS depends on its severity, complications, and absence or presence of pregnancy. The treatment involves dealing with electrolytic imbalance, hemodynamic changes, liver dysfunction,

pulmonary manifestations, hypoglobulinemia, febrile morbidity, thromboembolic events, adnexal torsion, and neurological manifestations [24-28].

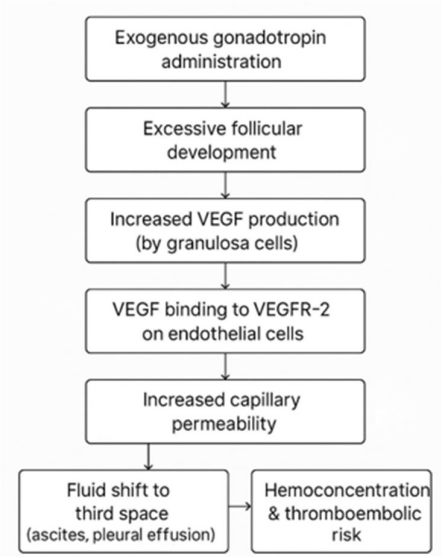

Fig 2: Mechanism of OHSS: role of VEGF and increase vascular permeability

Clinical manifestations and classification

The main event in the pathogenesis of OHSS is ovarian enlargement, secretion of vasoactive substances, ascites, and hypovolemia resulting from an acute extravasation of fluid into the interstitial space. OHSS is classified into 4 categories based on the severity of symptoms, signs, and laboratory findings.

- ✓ Mild ovarian hyperstimulation syndrome: It is defined by the enlargement of bilateral ovaries with multiple follicular and corpus luteal cysts, measuring up to 8 cm and accompanied by abdominal bloating and mild abdominal pain.
- ✓ Moderate ovarian hyperstimulation syndrome: It is characterized by the enlargement of the ovaries up to 12 cm, accompanied by abdominal bloating due to an increase in ovarian size and gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea) as well as ultrasound evidence of ascites. A rapid weight gain of over 3 kg might be the initial sign of moderate hyperstimulation.
- ✓ Severe ovarian hyperstimulation syndrome: About 2% of OHSS cases are classified as severe. The severe form is described by the presence of large ovarian cysts (>12×12 cm), clinical ascites with or without hydrothorax, hyperkalemia (potassium >5 mmol/L), hyponatremia (sodium <135 mmol/L), hypo-osmolarity (osmolarity <282 mOsm/kg), hypoproteinemia (serum albumin <35 g/L), oliguria (<300 mL/d or <30 mL/h), creatinine 1.1-1.5 mg/dL, and hypovolemic shock. Hemoconcentration with hematocrit >45%, white cell count >15000, liver dysfunction, increased blood viscosity, and thromboembolic events occurs in the most severe cases.
- ✓ Critical ovarian hyperstimulation syndrome: It is diagnosed when there is severe ascites or hydrothorax, hematocrit >55%, white cell count >25000/mL, oliguria or anuria, creatinine ≥1.6 mg/dL, creatinine clearance <50 mL/min, thromboembolism, or acute respiratory distress syndrome.

Suggestions for the assessment and monitoring of hospitalized patients with ovarian hyperstimulation syndrome:

- Vital signs (every 2-8 h, according to clinical status)
- Complete physical examination (daily, avoiding bimanual pelvic examination)
- Weight (recorded daily)
- Abdominal circumference (at the navel, recorded daily)
- Ultrasound evaluation of ascites and ovarian size (repeated as necessary to guide management or paracentesis)
- Daily monitoring of fluid intake and output
- Pulse oximetry (for patients with symptoms of pulmonary compromise)
- Chest X-ray and echocardiogram when pleural or pericardial effusion is suspected (repeated as necessary)
- Pregnancy test
- Electrolytes (daily)

- Complete blood count (daily, or more often as needed to guide fluid management)
- Liver enzymes (repeated as necessary)
- Serum creatinine or creatinine clearance and urine specific gravity (repeated as necessary) [29-35].

Medical treatment

- Circulatory Volume and Electrolyte Correction in OHSS: The primary focus in managing OHSS (Ovarian Hyperstimulation Syndrome) is to stabilize the circulatory (intravascular) volume and correct any electrolyte imbalances. It's essential to maintain proper blood volume to ensure good kidney function.
- Fluid Replacement: Treatment begins with intravenous (IV) administration of crystalloid fluids (such as normal saline or dextrose-containing saline) at a continuous rate of 125–150 mL/hour. In cases of dehydration or significant fluid loss, a rapid bolus of 500–1000 mL may be given initially. Fluids should be carefully titrated to maintain a urine output of at least 20–30 mL/hour and to improve hemoconcentration (thickened blood due to fluid loss).
- Type of Fluids Preferred: Among crystalloids, 5% dextrose in normal saline is preferred over lactated Ringer's, as it better supports intravascular volume without worsening fluid accumulation in the abdomen (ascites).
- Plasma Volume Expanders: In more severe cases, colloid solutions may be used to pull fluid back into the blood vessels. These include: albumin, mannitol, dextran, hydroxyethyl starch (HES), fresh frozen plasma. These agents give oncotic pressure (the pressure exerted by proteins to retain fluid in blood vessels), reducing the severity of hypovolemia (low blood volume) [36-39].

Advance therapeutic developments in iatrogenic OHSS

Advances in reproductive medicine have not only enhanced the success rates of assisted reproductive technologies (ART) but have also allowed for major improvements in managing complications such as iatrogenic ovarian hyperstimulation syndrome (OHSS). The contemporary approach emphasizes prevention and early intervention, particularly in high-risk patients, by using safer stimulation protocols, tailored medications, and strategic embryo transfer planning.

1. Shifting Toward Safer Stimulation Regimens

One of the most significant innovations in managing OHSS risk is the move away from hCG-based ovulation triggers. Traditional use of hCG was associated with sustained luteotropic effects and increased capillary permeability. By contrast, GnRH agonists, when used in antagonist protocols, offer a safer alternative by providing a short surge of endogenous LH without prolonging VEGF stimulation, thereby markedly reducing the likelihood of OHSS. The antagonist cycle also provides flexibility in cycle cancellation and reduces the hormonal load, contributing further to safety.

2. Cabergoline and VEGF Modulation

Targeting the VEGF pathway has emerged as an important pharmacologic strategy. Cabergoline, a dopamine D2 receptor agonist, is now commonly employed to reduce the severity of early OHSS. It works by dampening VEGF-induced vascular permeability one of the primary mechanisms driving fluid shift into third spaces. Compared to traditional measures like albumin infusions, cabergoline is easier to administer, more targeted, and has shown promising results in multiple clinical settings.

3. Withholding Embryo Transfer: "Freeze-All" as a Safety Net

When a patient exhibits signs of excessive ovarian response during stimulation, the freeze-all approach-deferring embryo transfer and cryopreserving embryos for use in a later, unstimulated cycle-serves as an effective preventive strategy. This eliminates the synergistic effect of pregnancy-related hCG on OHSS, particularly in its late form. Improved cryopreservation outcomes have made this method increasingly reliable without compromising pregnancy success rates.

4. Supportive Care Techniques in Moderate to Severe Cases

Once OHSS develops, the current therapeutic direction is to support the patient conservatively while avoiding unnecessary hospitalization. Outpatient drainage of ascitic fluid, when indicated, provides symptom relief, while fluid management using colloids and crystalloids, along with close monitoring of hematocrit and renal function, prevents further deterioration. Anticoagulant therapy, such as low molecular weight heparin, is critical in preventing thromboembolic complications, which remain a major risk in severe OHSS cases due to hemoconcentration.

5. Individual Risk Stratification and Personalized Protocols

Risk profiling using baseline markers such as anti-Müllerian hormone (AMH) levels and antral follicle counts (AFC) allows clinicians to pre-emptively identify individuals at higher risk of OHSS. Modern protocols are increasingly patient-centered-adjusting gonadotropin doses and timing based on follicular response and hormone dynamics during stimulation.

6. Research Frontiers and Novel Molecular Targets

Emerging therapies are exploring alternatives beyond VEGF. Agents targeting the angiopoietin–Tie2 pathway, selective estrogen receptor modulators, and monoclonal antibodies that interfere with vascular permeability are under investigation. These offer a future direction for refining therapy, especially for those in whom conventional measures fail [40-45].

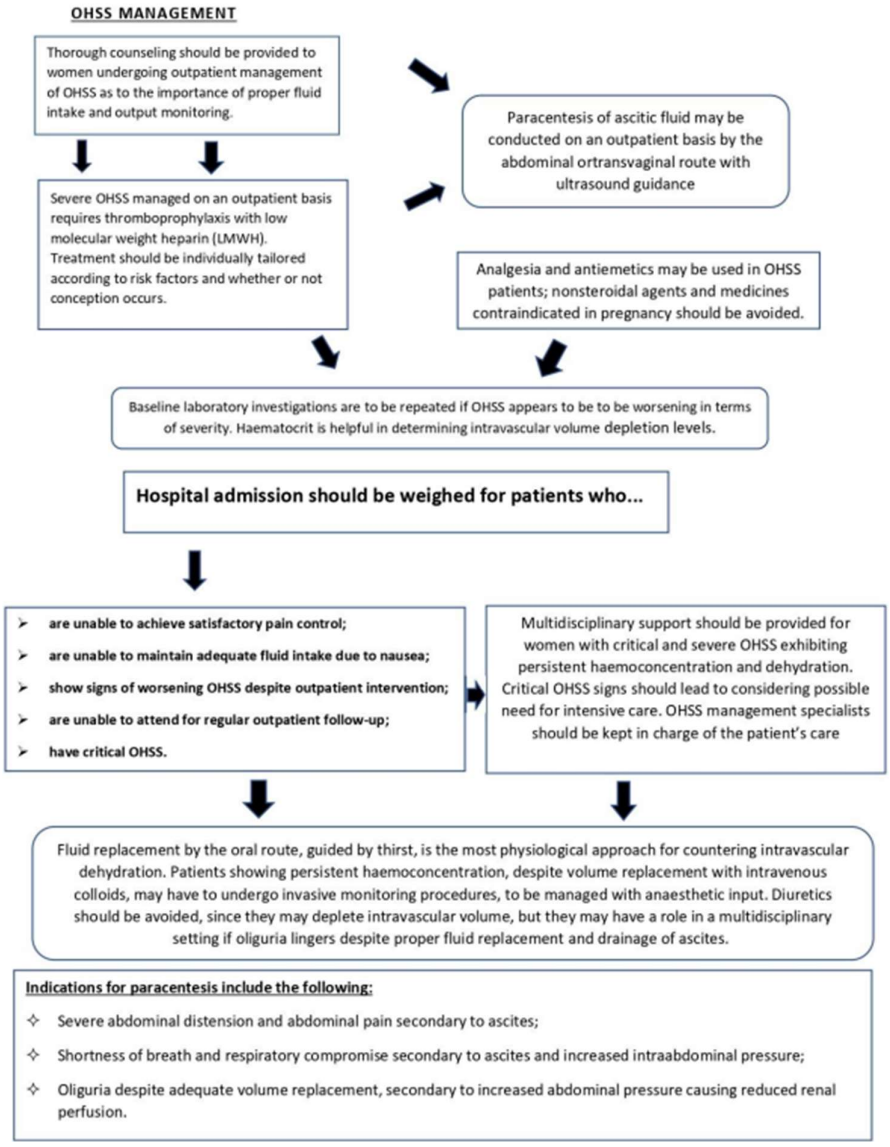

Fig 3: Flowchart outlining evidence-based management pathway for OHSS patient

CONCLUSION

Ovarian Hyperstimulation Syndrome remains a significant, yet preventable, iatrogenic complication of assisted reproductive technologies. Understanding the multifactorial pathophysiology-particularly involving increased vascular permeability mediated by VEGF-has led to improved diagnostic and management strategies. Early identification using clinical features, biomarkers such as AMH and estradiol, and ultrasound findings can help stratify patients by risk. Advances in therapeutic interventions, including outpatient paracentesis, tailored anticoagulation with LMWH, and individualized fluid replacement strategies, have shifted the focus toward safer, evidence-based management. Furthermore, the incorporation of preventive approaches-such as GnRH agonist triggers, dopamine agonists, and freeze-all protocols-has notably reduced the incidence of severe OHSS.

Continued research, especially post-2023, emphasizes multidisciplinary care and monitoring to optimize outcomes. Proper patient education, personalized protocols, and timely escalation of care remain the cornerstone of managing OHSS and preserving fertility outcomes. Ongoing research beyond 2023 underscores the importance of multidisciplinary clinical coordination, vigilant hemodynamic monitoring, and individualized patient management in mitigating the morbidity associated with OHSS. Patient-centered education, protocol-driven ovarian stimulation, and timely escalation to tertiary care services constitute the fundamental pillars in optimizing therapeutic outcomes and safeguarding reproductive potential.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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