Ovarian hyperstimulation syndrome: an overview and prevention approaches

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Abstract
Background
Ovarian hyperstimulation syndrome (OHSS) occurs as a consequence of prompt during the luteal phase of ovulation. The syndrome manifests primarily as ascites and pleural effusion, with pericardial effusion occurring rarely. Severe forms accompanied by electrolyte changes, cardiac, hepatic, renal, and hemodynamic problems linked with increased thromboembolic risk.

Main body
Inflammatory mediators, human chorionic gonadotropin, and vascular endothelial growth factor are all included in the pathophysiology of Ovarian hyperstimulation syndrome. Many risk factors affect the syndrome such as body weight, polycystic ovary syndrome, previous OHSS, estradiol level, etc. There are primary and secondary prevention methods to reduce the occurrence of the syndrome.

Conclusion
In GnRH antagonist cycles, gonadotropin-releasing hormone (GnRH) agonist trigger & GnRH agonist triggering have been identified as the most efficient measures for OHSS prevention. Coadministration of dopaminergic agonist & mild ovarian stimulation was demonstrated to be safe & efficacious.

Keywords: Ovarian hyperstimulation, Human chorionic gonadotropin, GnRH agonist, GnRH antagonist, and Estradiol.
Introduction
Ovarian hyperstimulation syndrome is the potentially fatal iatrogenic side effect of luteal phase ovulation stimulation. This syndrome is characterized by numerous cysts increasing the ovarian size and vascular permeability, ascites, pleural effusion, and pericardial effusion which may also accompanied by electrolyte changes, in addition to cardiac, hepatic, renal, and hemodynamic problems with increased thromboembolic risk. The usage of gonadotropins to promote ovulation has been reported to cause this condition [1].

Main text
Pathophysiology
Enhanced capillary permeability & arteriolar vasodilation are the two primary features of Ovarian hyperstimulation syndrome that lead to fluid leakage from vessels into the 3rd space, causing hypovolemia (Fig. 1). Vasoactive and proinflammatory cytokines cause enhanced ovarian volume & permeability of capillary [2].

In Ovarian hyperstimulation syndrome, patients may have elevated concentrations of some interleukins. Interleukin-6 expression, for instance, is linked to hemoconcentration, increased capillary permeability, elevated plasma estrogen levels, and suppression of albumin formation [3].

Vasoactive-angiogenic chemicals are produced during HCG follicular development, such as vascular endothelial growth factor (VEGF), and are considered the main stimuli in susceptible patients [4]. VEGF receptors may only be present in the corpus luteum vasculature before stimulation and might be present all over the corpus luteum after HCG stimulation. Both VEGF and VEGF receptors reach peak expression within 48 hours after stimulation.

Enlargement of Bilateral ovarian & 3rd-space fluid shift are additional features of OHSS. The sudden changes in body fluids lead to hemoconcentration with decreased organ blood flow, changes in blood coagulability, an increased risk of thrombosis, and fluid leakage into the peritoneal cavity and lungs [5].
Epidemiology
An early cohort of in vitro fertilization (IVF) cases had a rising trend in the prevalence of severe OHSS, rising from 0.06 percent in 1987 to 0.24 percent in 1996 [7]. In a second study, which followed a global rise in the number of IVF cycles, it was discovered that severe Ovarian hyperstimulation syndrome requiring hospitalization increased from 0.9 to 1.8 percent over a year [8]. Between 3-6% and 0.1-2% of moderate and severe cases were observed respectively in IVF patients across different studies [9]. Since the 2000s, there has been a reduction in the occurrence of moderate to severe OHSS cases when at-risk individuals were induced for oocyte final maturation using GnRH agonists. The Japanese registry analyzed 1,435,108 cycles of assisted reproductive technology (ART). During the analysis, they identified 11,378 cases of moderate to severe instances related to Ovarian hyperstimulation syndrome, which accounts for 0.79 percent of all cycles[10].
Mathur et al. examined 4894 consecutive assisted reproductive technology cycles and revealed 51 incidences of OHSS, (all Ovarian hyperstimulation syndrome cases received [HCG] for triggering final oocyte maturation). Final oocyte maturation was induced using GnRH agonists in another seventy-one patients that were deemed high risk for the syndrome, resulting in no cases of Ovarian hyperstimulation syndrome in these cases [11].

Clinical signs & classification
The syndrome can be categorized into two types, based on when the symptoms begin to appear. Early OHSS takes place within 3 to seven days subsequent to HCG trigger. Late OHSS arises
within twelve to seventeen days following the HCG trigger [12]. OHSS is divided into 4 stages (as shown in Table 1).

**Mild OHSS**
This stage is distinguished by enlargement of ovarian on both sides, slight diarrhea, mild vomiting, or minor nausea. There are no biochemical anomalies.

**Moderate OHSS**
In this stage, an ultrasound examination reveals ascites and enlarged ovaries.

**Severe OHSS**
In this stage, Fluid can be detected in the pericardial and pleural cavities which can cause hypovolemia and significant respiratory distress. Impairment of liver function due to decreased hepatic perfusion; anticoagulating factors are among the first to be depleted. [13]. Hematocrit up to forty five percent , hyponatremia, and hyperkalemia also occur .

**Critical OHSS**
In this stage, essential organs are at high risk including venous, arterial thrombosis, and acute renal failure. Pleural effusion develops into a significant hydrothorax and is accompanied by pericardial effusion. The clinical picture may become even more complicated in cases of acute respiratory distress syndrome [14].

**Associated complications:**
- An increase in ovarian size can lead to a condition known as ovarian torsion. In such cases, surgery may be required to correct the problem.
- Thromboembolism: although uncommon, it is one of the most dangerous OHSS consequences. Thrombosis can be either arterial (25%) or venous (75%), and it can result in death or severe brain damage [15]. These occurrences are probably related to both hemoconcentration and hypercoagulation that result from the increased serum estrogen levels [16].

There have been reports of thromboembolic OHSS consequences in the internal jugular and other arteries. It was reported in two cases in which the women had not previously experienced Ovarian hyperstimulation syndrome, but they had an underlying thrombophilia, and in three cases in which the female had experienced intense Ovarian hyperstimulation syndrome but no underlying thrombophilia [17].

Some specialists recommend prevention, such as low-dose heparin medication, before ovulation induction for women who have an underlying thrombophilia (such as antithrombin III deficiency), to prevent thromboembolic consequences [18].
By recognizing female at risk, numerous preventive interventions have been recommended to reduce the incidence of the syndrome; these strategies can be categorized as primary or secondary.

**Primary prevention**

**GnRH Antagonists**

Gonadotropin-releasing hormone antagonists’ usage can stop LH release through COH without causing the negative effects of agonists [21]. In comparison the safety & effectiveness of GnRH antagonists to the long stimulation regimen GnRH agonists, it was found that the GnRH antagonist group had a statistically significant reduction in the frequency of OHSS [22].
Therefore, female having IVF or Intracytoplasmic sperm injection (ICSI) cycles and high risk of developing severe OHSS should follow the short GnRH antagonist protocol [23].

**Mild Ovarian Stimulation**

The advantages of mild stimulation include stress reduction [24] and financial benefits [25]. In order to reduce the number of oocytes and avoid Ovarian hyperstimulation, the ovaries are stimulated using mild stimulation, which involves the use of gonadotropins and/or oral drugs such as letrozole or clomiphene citrate [26]. Datta et al verified that OHSS risk is decreased in patients who receive gonadotropin doses that are equal to or less than one hundred & fifty international unit per day as compared to subjects who receive greater gonadotropin doses (greater than 150 IU) in both normal and hyper-responders. On the other hand, no significant impact was observed in patients who are bad responders [27].

**In Vitro Maturation (IVM)**

IVM is the process of removing immature oocytes from the germinal vesicle stage, which may or may not involve gonadotropin exposure. After that, they develop in vitro until getting to the metaphase II stage at which point, they are prepared for fertilization. IVM may decrease the risk of the syndrome in females with PCOS. [28]. Treatment is still regarded as experimental, and there is not enough information available to support recommendations for IVM prior to IVF or ICSI [29].

**Secondary prevention**

**GnRH Agonist Trigger in GnRH Antagonist Cycles**

The gold standard for ovulation induction and final oocyte maturation in cycles of ART has historically been a bolus of HCG. Protocols including GnRH antagonists were developed to stop an early LH surge. As an alternative to HCG, it became possible to stimulate ovulation and ultimate oocyte maturity with a GnRH agonist. Subcutaneous injection of midcycle single bolus of GnRH agonist is an option (0.2 to 0.5 milligram of leuprorelin, triptorelin, or buserelin) [26].

**Coasting**

Coasting successfully lowers the risk of OHSS. It involves suspending gonadotropin and retarding the administration of HCG until the blood estradiol level has significantly decreased [30]. Nevertheless, there was not enough data to evaluate the process's effectiveness in terms of live birth and clinical pregnancy [31].

**Low doses of HCG for complete oocyte maturity.**

The typical dose of HCG is nearly 5000 or 10,000 IU and it is considered a cause of OHSS development [32]. Therefore, it has been proposed that lower HCG dose reduce the chance of OHSS in unexpected hyper-responders during a long GnRH agonist regimen [26]. However, using very small HCG dose, two thousand international unit, would undoubtedly affect mature oocytes number; however, women who receive five thousand international unit or ten thousand international unit of HCG do not appear to have a different incidence of severe OHSS [26].

**Cycle Cancellation (HCG Withholding)**

Cycle cancellation causes financial and emotional difficulties, especially for cycles that would not have developed into clinical OHSS [33]. The cycle should be terminated only in cases of severe OHSS as a last option because there are safer therapies such as GnRH antagonist–gonadotropin-releasing hormone agonist trigger and freeze-all policy [34].

**Elective cryopreservation (freeze-all strategy)**
Embryo freezing was one of the earliest methods used to stop or lower the risk of OHSS. Any embryos that are not transferred should be cryopreserved as this could decrease hCG production and, as a result, the early OHSS form [12]. According to a major multicenter RCT, a higher live birth rate and a lower incidence of OHSS were associated with frozen embryo transfer [35].

Drugs
Calcium gluconate
- **Mechanism of action in OHSS**
  Arterial dilatation & enhanced permeability cause body fluid movement from intravascular to extravascular regions resulting in hypovolemia that increases the aldosterone level by renin-angiotensin system activation [4]. Additionally, the levels of both extracellular and intracellular calcium are inversely correlated with renin secretion from the kidney [36] so, acute calcium-sensing receptor activation suppresses renin release and lowers VEGF[37].
- **Dose**
  200 ml of physiologic saline with 10 ml of a 10% calcium gluconate solution added over 40 minutes, this infusion is started within 30 minutes of ovum collection, and continued for 3 days [38]. The risk of syndrome is reduced by intravenous calcium without having an impact on the pregnancy rate [39]. Gurgan examined the effects of intravenous calcium infusion on polycystic ovary syndrome patients in OHSS prevention & concluded that IV calcium infusion lowers OHSS risk in high-risk individuals [40].
Cabergoline
Cabergoline is a long-acting dopamine receptor agonist used for the treatment of hyperprolactinemic conditions, acromegaly, Cushing disease, lactation inhibition, and OHSS [41], [42].
- **Mechanism of action in OHSS**
  Cabergoline acts by dephosphorylation of the VEGF -2 receptor thus attenuating vascular permeability [43].
- **Dose**
  0.5 mg orally daily for eight days after hCG triggering [44].
A study examined women undergoing assisted reproduction who took the previous dose of Cabergoline or a placebo beginning on hCG trigger day and found that there were 43.8 percent of mild OHSS cases in placebo group in comparison to 20 percent in Cabergoline group [43]. Another study on Cabergoline against control in 40 high-risk women illustrated that moderate OHSS incidence declined to 15% in cabergoline-treated group compared with 50% incidence in the control group [45].
Diosmin
It is a bioflavonoid that can be produced from hesperidin or extracted from various plants. It is used to treat capillary fragility, insufficient venous return, and chronic venous insufficiency. Diosmin has a good safety profile and is easily accessible over the counter [46].
- **Mechanism of action in OHSS**
Micronized purified flavonoid fraction (MPFF) is a semi-synthetic drug that contains ninety percent micronized diosmin and ten percent hesperidin [47]. MPFF has a venotonic impact that reduces venous reflux and relieves edema by facilitating efficient venous drainage [48]. Diosmin also prevents the release of the inflammatory mediators thromboxane A2 & prostaglandin E2 [49]. The synergistic effect of the flavonoids present in MPFF’s composition is demonstrated by the fact that MPFF reduces vascular permeability more than its separate components [50].

- **Dose**
  2 tablets (500mg) three times daily for 2 weeks beginning on the day of HCG injection [51].
  Saad and Khalil studied two groups, group I received cabergoline and two tablets of diosmin (500 mg) three times daily starting on HCG trigger day, group II received Cabergoline only revealed that OHSS incidence reduced in group I than in group II (7.3% versus 16.2%, respectively) [51].

**Hydroxyethyl starch (HES)**
Hydroxyethyl starch is a group of synthesized colloids made from amylopectin, a starch found in potatoes or maize that resembles glycogen [52].

- **Mechanism of action in OHSS**
  Its high molecular weight (exceeding 200,000 kDa) results in a reduction in blood viscosity, as well as an enhance in both osmotic pressure & intravascular volume. [53]. Additionally, HES lessens blood coagulation and suppresses platelet aggregation, which finally stops the development of OHSS[54].

- **Dose in OHSS**
  A volume of one thousand milliliters of six percent HES is given on oocyte retrieval day [55].

**Metformin**
Metformin increases insulin sensitivity, lowers hyperinsulinemia, and inhibits the excess androgen production in the ovary in PCOS [56].

- **Mechanism of action in OHSS**
  Metformin reduces the levels of vascular endothelial growth factor, insulin, & E2 on HCG-triggering day [57]. In a study that compares a group that received metformin to the placebo group, it was found that metformin had a significant impact on decreasing the risk of OHSS, with the risk dropping from 27 percent to (6-15) percent. [56].

**Clomiphene citrate (CC) and/or letrozole**
It has been recommended that a combination of CC and/or letrozole with gonadotropins lowers the risk of syndrome.

- **Mechanism of action in OHSS**
  Clomiphene citrate acts on the hypothalamus by competition for estrogen receptors that stimulate endogenous FSH and LH secretion. As a result, during ovarian induction with gonadotropins, the growth of dominant follicles is reduced [58]. Letrozole functions by stimulating endogenous FSH and LH production, while simultaneously restraining the conversion of androgens into estrogens in ovarian granulosa cells leading to a decrease in circulating estradiol levels without affecting the estrogen receptors in peripheral tissues. [58].
  A study found that administering CC or letrozole reduced the risk of OHSS in poor & normal-responder cases during GnRH agonist & gonadotropin-releasing hormone antagonist co-treated cycles. Regarding live births and clinical pregnancy rates, there was no discernible difference. In
the overall population, there were fewer oocytes recovered [59]. The certainty of evidence (CoE) was rated as low, & the evaluation of quality indicated a moderate level [59].

Palomba et al have identified the most effective methods for blocking & decreasing the occurrence & severity of OHSS in in vitro fertilization cases and discovered that GnRH agonist trigger in gonadotropin-releasing hormone antagonist cycles & gonadotropin-releasing hormone agonist triggering emerged as the most efficacious interventions for blocking Ovarian hyperstimulation syndrome with a moderate certainty of evidence, even though elective freezing of embryos exhibited a low certainty of evidence. Additionally, the usage of mild ovarian stimulation, and dopaminergic agonists coadministration proved to be safe & effective with a moderate certainty of evidence [30].

Conclusion
OHSS is a negative consequence of gonadotropin prompt that can be fatal. The primary indicators of Ovarian hyperstimulation syndrome arise due to enhanced capillary permeability and arteriolar vasodilation. Primary risk factors include low body weight, young age, polycystic ovary syndrome & previous Ovarian hyperstimulation syndrome while secondary factors include elevated E2 level above 3,000 pg/ml, enhanced number of preovulatory follicles & retrieved oocytes. There are several methods for prevention of OHSS such as short GnRH antagonist protocol in high-risk female, using of gonadotropins and/or letrozole or CC as mild stimulation, GnRH antagonist cycles accompanied by gonadotropin-releasing hormone agonist as trigger with dose of 0.2 to 0.5 mg. Moreover, using lower dose of HCG is safer as 5000 IU or 10,000 IU do not have different incidence of severe OHSS. HCG withholding is considered the last option in case of sever OHSS. Freeze-all strategy helps to decrease HCG production and OHSS to form. It was found that gonadotropin-releasing hormone agonist trigger in gonadotropin-releasing hormone antagonist cycles and GnRH agonist triggering are the most efficient interventions for prevention with a moderate certainty of evidence, additionally, there are many drugs that prevent the syndrome and many studies found that mild ovarian stimulation and dopamine agonists are efficient and safe with a moderate CoE.

References
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