Review article

Ovarian Hyperstimulation Syndrome: A Review of Clinical Feature, Pathophysiology, Risk Factors, And Prevention.

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Abstract

Ovarian hyperstimulation syndrome is a dangerous complication of ovulation induction during infertility treatment by gonadotropins stimulation and human chorionic gonadotropin injection. Increased capillary permeability, causing fluid leakage from the intravascular compartment, with the accumulation of fluid in the third-space and consequent intravascular dehydration, is the main change in the pathophysiology of ovarian hyperstimulation syndrome. Vascular endothelial growth factor is the main mediator in the development of ovarian hyperstimulation syndrome. The recent application of new modalities: Gonadotropin-releasing hormone antagonist protocol, Gonadotropin-releasing hormone agonist triggering of ovulation and embryo/oocyte vitrification, facilitates the elimination of ovarian hyperstimulation syndrome associated with controlled control ovarian hyperstimulation for IVF program. In this manuscript, we reviewed the pathophysiology, clinical features, predisposing factors, and both primary and secondary arrangement for preventing ovarian hyperstimulation syndrome as there is no single measure to prevent OHSS totally. Therefore, categorizing the women based on their risk potentiality seems to be beneficial to direct the line of management as early as possible to avoid the emergence of ovarian hyperstimulation syndrome.

Keywords: controlled ovarian hyper-stimulation, ovarian hyperstimulation syndrome, in vitro fertilization.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic serious clinical complication with controlled ovarian stimulation (COS). It is detected in about 1-5 percent of treatment cycles. COS is used to grow numerous ova during assisted reproduction cycles in order to enhance the harvested ova numbers. OHSS, on the other hand, is an excessive reaction to this procedure [(1,2)]. Ovarian enlargement, hypercoagulability, hemoconcentration, ascites, and electrolyte imbalance are all symptoms of the syndrome. It causes nausea, vomiting, diarrhea, abdominal distention and discomfort, and dyspnea in patients. Acute renal failure, venous thromboembolism, and pleural effusion are all signs of a serious clinical condition 3OHSS is linked to the use of gonadotropins during COS. However, in some circumstances OHSS has been reported to occur spontaneously in conjunction with the help of either gonadotrophin-releasing hormone or clomiphene 4,5.

This review aims to discuss the latest updates in the pathophysiology to determine its risk factors, clinical presentation, and the most recent ways of prevention.

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Pathophysiology

The increase in vascular permeability is the major physiological change behind the OHSS, leading to shifting of fluid from the intravascular space to the third space compartment. An important mediator of OHSS is the Pro-angiogenic vascular endothelial growth factor (VEGF). Serum level of VEGF has been found to correlate with severity of OHSS [6]. The VEGF interacts with the VEGF receptor-2 (VEGFR-2), this interaction promotes angiogenesis and vascular hyperpermiability. The over expression of VEGF characterizes the increased vascular permeability seen in OHSS[7]. Granulosa cells secret the VEGF, and its secretion is stimulated by human chorionic gonadotropin (hCG). The higher levels of VEGF resulting in sever form of OHSS [8]. The exposure to hCG is key factor of the syndrome; when hCG is not used as an ovulatory trigger during COS, the OHSS does not occur, whereas increasing hCG exposure increases the incidence of OHSS [2,9]. The action of hCG in OHSS can be explored through two clinical presentations: the "early" form and the "late" form. The action of exogenous hCG on the hyper stimulated ovarian by gonadotropins causes early OHSS, which emerges during the first 9 days after hCG therapy as an ovulation trigger. The late OHSS, take place after10 days of using hCG as a trigger of ovulation and represents the ovarian response to endogenous hCG generated by the trophoblast [10].

Another mechanism implicated in the pathogenesis of OHSS is the intraovarian renin angiotensin system (RAS). Vascular permeability, endothelial proliferation, angiogenesis, and prostaglandin production are all regulated by the ovarian RAS. hCG causes a significant stimulation of the RAS, as indicated by increased renin activity in the follicular fluid of women with OHSS [7, 11]. Overstimulation of this cascade, in combination with high VEGF levels, is hypothesized to potentiate OHSS synergistically [12,13]. Epidermal growth factor, insulin-like growth factor, basic fibroblast growth factor, platelet-derived growth factor, transforming growth factor alpha and beta, interleukin-1B, and interleukin-6 are some of the other variables that have been linked to the development and severity of OHSS [7,14]. A summary of the pathophysiology is illustrated in figure (1).

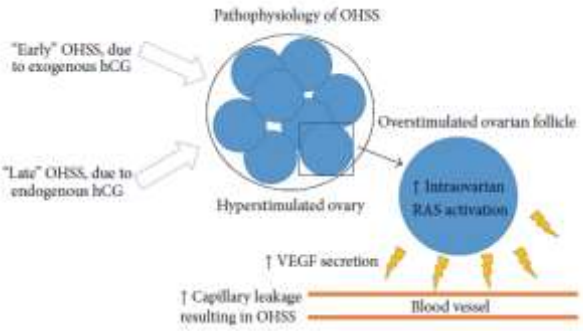

Figure 1. a graphic representation of ovarian hyperstimulation pathophysiology [2].

Risk factors

Below are factors that independently increase the risk of OHSS [2,6,15,16]:

1. Low body weight.
2. Young age.
3. High exogenous gonadotropin doses.
4. The syndrome of Polycystic ovary (PCOS).
5. Previous history of OHSS.
6. High increasing estradiol (E2) level.

In addition, risk increase with an increasing number of small follicles (8–12 mm) during COS, luteal phase support after IVF with hCG instead of Progesterone, more than 20 oocytes retrieved during ova pick up, early pregnancy, and raised basal anti-Mullerian hormone (AMH) levels. Finally, ethnicity appears to play a factor, since research has indicated that African-American women undergoing IVF are more likely than Caucasian or Hispanic women to have OHSS [2,6].

Clinical presentation

The traditional clinical classification of OHSS is mild, moderate, and severe. Abdominal distention, transitory lower

abdominal discomfort, nausea, vomiting, and diarrhea15 are all common clinical symptoms of OHSS [2].

Because of the spike in endogenous hCG produced by early pregnancy, symptoms of OHSS may emerge as early as one day after the ovulation trigger with hCG, then become more severe over the next 7-10 days [6]. Finally, the condition progresses when symptoms persist, getting worse, and ascites appear as increased abdominal girth or seen by ultrasound evaluation. The illness is classified as severe if pain occurs with one of the following:

- Accelerated gain of weight
- Tense ascitic abdomen
- Unstable hemodynamic parameters (orthostatic hypotension, tachycardia)
- Difficulty in respiration (tachypnea)
- Worsening oliguria
- lab abnormalities [14].

Hemoconcentration, lower peripheral blood flow, and decreased activity as a result of stomach distension and discomfort enhance the risk of thromboembolism. Renal failure, thrombosis, adult respiratory distress syndrome (ARDS), and bleeding from ovarian rupture are all fatal consequences of OHSS [17].

Prevention of OHSS

Prevention measures for OHSS are widely described as primary and secondary. Primary prevention classifies people into high, average, or low risk for OHSS based on risk markers, and then assigns treatment programs to them based on that classification. Secondary prevention, addresses techniques utilized in individuals who have acquired an excessive response to ovarian stimulation throughout a cycle and are attempting to avoid development to OHSS [2].

Primary Prevention:

1. *Programs of ovulation induction:*

A likelihood of OHSS must be examined depend on the patient's medical history, examination, ultrasound findings, and antral follicle count (AFC) [18]. Patients with PCOS have an increased risk of OHSS. For ovulation induction in PCOS patients, the lowest dose of gonadotropin should be administered, and step-up regimens should be employed rather than step-down regimens. For ovulation induction, step-up regimens use a low dose of gonadotropin (75 IU). Only if a good ovarian response with follicles >10 mm has not been achieved after 14 days will the gonadotropin be raised. It continues after achieving the right dose until at least one follicle is ≥18 mm [19].

2. *Metformin:*

Metformin reduces the odds of OHSS by more than 60 percent and increases clinical pregnancies rate without reducing live birth rates, according to a recent study [20]. As a result, a daily dose of 1-2 g. for at least 8 weeks before COS was advised to prevent the OHSS[21]. This conclusion corroborated Palombo et al prior's systemic assessment, which found a considerably decreased OHSS rate after metformin administration [22].

3. *Aromatase inhibitors (AIs) for ovulation induction*:

These medications work by inhibiting cytochrome p450 enzymes, which reduce estrogen synthesis, example for this medication is anastrozole (Armidix) and letrozole (femara). As a result, they will boost folliculogenesis by increasing the pituitary gland's release of follicle-stimulating hormone. As a result, the negative feedback mechanism will be preserved, and the incidence of OHSS during ovulation induction will be reduced [23]. However, because a Cochrane Review found no difference in OHSS rates after AIs compared to other ovulation induction medicines, this class of pharmaceuticals is not commonly prescribed [24].

4. *Individualize treatment programs for in- vitro fertilization*:

Individualized COS (iCOS) has been shown to reduce OHSS and cycle cancellation in humans. Gonadotropin administration should be individualized to each woman individually, based on her AFC and

AMH as biomarkers for predicting and preventing overresponse, and COS (e.g., FSH beginner dose or costumed GnRH antagonist protocol). This is achieved via an algorithm based on those indicators [2,25]; nonetheless, iCOS offers a promising option in preventing OHSS by individualized COS regimens and appears to be the primary step toward a near-term ART.

5. *ovarian drilling by Laparoscopy in PCOS cases*:

Laparoscopic ovarian drilling (LOD) sometimes called polycystic ovary cauterization is thought to be an alternative to ovarian stimulation for increasing ovulation. The main advantage of LOD is that it cuts down on the amount and duration of gonadotropins required for ovulation induction. Slim ladies with elevated serum levels of luteinizing hormone (LH) [26] have had the best results.

6. Alternatives of human chorionic gonadotropin for ovulation triggering:

When choosing the appropriate medicine for initiating the ultimate maturation of follicles, the risk of OHSS development should be considered. An important thing to remember is that there is no agent that can eliminate the OHSS risk. For a long time, the exogenous hCG has been used to induce LH surge. Its lengthy half-life results in long autotrophic effects, numerous corpora formation, and increased progesterone and E2 levels in the luteal phase. LH shows a half-life of 1 hour, but hCG showed a half-life > than 24 hours [27].

Below are some measures used to reduce or avoid using human chorionic gonadotropin for ovulation induction:

a) *Human chorionic gonadotropin Reduction of doses*:
It was proposed that if the serum estradiol level was greater than 3000 g/ml, the hCG dose should be cut in half (5000 IU). There is still no clear consensus on it.[28]. It was noted that the administration of lower hCG dose for ovulation trigger had not implicated clinical outcome and questions still over its ability to reduce the OHSS risk [29].

b) *Gonadotropin-releasing hormone agonist (GnRHa):*
in contrast to hCG, GnRHa induces a shorter gonadotropin surge in the mid-cycle (for 24-36) by stimulating the secretion of pituitary LH. When GnRHa triggering was employed in conjunction with a GnRH anagonist IVF technique, the likelihood of OHSS was almost minimized in a freeze-all protocol for highly risky women [30]. Furthermore, when compared to traditional hCG triggering cycles, several studies show that the rates of continued pregnancy are low [31].

c) Recombinant Luteinizing Hormones (rLH):
The use of rLH to imitate the endogenous LH peak in 12-hour half-life is merely a potential method for preventing OHSS in high-risk patients. A study made by Youssef and colleagues didn't mention any difference between urinary LH and recombinant HCG [32]. rLH, on the other hand, has been linked to a low pregnancies rate and a reduced cost-benefit ratio [33].

6. *Gonadotropin-releasing hormone antagonists as substitutes to long agonists IVF protocols:*
After completing GnRH antagonist treatments, patients with a high risk of OHSS have been demonstrated to have a decreased risk [34]. However, in the early years, there were questions over the benefit and the pregnancy rate of the antagonist protocols; however, GnRH antagonist programs are now the most effective [35].

Secondary preventions

These should be considered in patients who already have an overresponse to COS. The purpose of intervention at this stage is to prohibit the progression to OHSS.

1. Coasting or delaying the hCG administration:
In patients with many follicles developed or dangerously elevated E2 level is reached,

hCG triggering could be delayed until the E2 levels decrease or plateau [34,35]. Then, gonadotropin injection should be stopped during the coasting period. After the gonadotropin cessation, mature follicles continue growing for four days and the E2 levels for 1-2 days. Coasting should not last > 4 days to prevent decrement in pregnancy rate, which is expected following a more extended period of cessation [36]. Coasting is widely involved as a first-line secondary prevention measure by clinicians [2]. Still, there are controversies about this action [37]. D'Angelo et al. identified 4 RCTs that reported that there was the same incidence of both moderate and severe OHSS with coasting. In addition, fewer oocytes were picked up from the coasting group, for that they did not recommend it, since it did not show a benefit of coasting in comparison to other interventions [38]

2. Cryopreservation of all embryos:

According to studies, the best way to avoid OHSS is to utilize a GnRHa trigger and then cryopreserve all embryos. In a Cochrane Review comprising two randomized controlled trials [38], there is still insufficient evidence to warrant routine cryopreservation [38,39].

3. Cycle cancellation:

Suspending the ovulation triggering by hCG in GnRHa IVF protocols when ultrasound scanning reveal multiple follicles with elevated estrogen levels is the greatest definite approach to avoid the OHSS [40]. For intrauterine insemination and IVF cycles, the estradiol critical value for stopping hCG from preventing OHSS was reported to be 2000 pg/mL and 4000 pg/mL, respectively [41,42].

Alternative methods of prevention:

1. Albumin:

Intravenous albumin is hypothesized to limit the creation of other compounds that cause OHSS by preventing the release of vasoactive material from the corpus luteum. Albumin's oncotic action helps keep intravascular volume stable and prevents hypovolemia, hemoconcentration, pleural effusion, and ascites [43,44]. However, the side effect of albumins, such as allergic reaction and virus transmission, should be kept in mind [45], and it can't be used routinely [43]. Prophylactic intravenous albumin did not diminish the incidence of severe OHSS or the pregnancy rate, according to a systematic review published in 2010.

2. Calcium:

Calcium infusion could prevent severe OHSS, according to Naredi and Karunakaran; the impact was comparable to cabergoline [47].

3. Hydroxyethyl starch solution (HES):

Despite the fact that the HES solution is a competent volume expander and possibly more successful than the albumin, the effectiveness of HES in contrast to albumin must be reevaluated based on numerous research [48].

4. Dopaminergic agonist preventing ovarian hyperstimulation syndrome (cabergoline):

Increased capillary permeability is caused by VEGF during ovarian hyperstimulation by the VEGF receptor 249,50, which is the major cause of OHSS. A dopamine agonist named Cabergoline that is expected to effectively decrease the occurrence of moderate OHSS while having no effect on clinical pregnancy or loss rates [51]. A study tried to determine cabergoline ability to prevent OHSS and its effect on the outcome of assisted reproductive technology (ART) like implantation and pregnancy rates. Their result showed that cabergoline was safe with good ART outcomes [49], it was recommended to be started alongside hCG triggering with starting dose of 0.5mg /total of eight days [52].

5. Low-dose aspirin:

Platelet hyperstimulation that occurs with OHSS may be caused by supraphysiological ovarian stimulation. So low-dose aspirin treatment may decrease the severe OHSS risk [53].

6. In vitro maturation (IVM) of immature oocytes:

IVM is another alternative way for fertility treatment in patients with an exaggerated ovarian response with a high risk of OHSS [(54)]. During ovarian stimulation, the harvest of the mature and immature oocytes, followed by IVM, would effectively avoid OHSS [(55)].

Conclusion

Carful primary estimation of the condition of infertile couples, early detection of the OHSS risk factors, and effective application of the primary preventive strategies can make OHSS-free clinics feasible. The prevention of severe OHSS is still possible even after the ovulation induction in most patients by adequate monitoring, diagnosis of ovarian hyperresponsiveness earlier, together with appropriate management. Severe OHSS was once thought to be an iatrogenic fetal syndrome. However, it may now be effectively prevented and treated in its early stages. This achievement represents a significant advancement in the inducement of ovulation and the treatment of infertility.

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