Ovarian Hyperstimulation Syndrome (OHSS): Pathogenesis and Prevention

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8.1 Introduction

Ovarian hyperstimulation syndrome (OHSS) is the least prevalent, albeit the most serious complication of ovulation induction. OHSS is a syndrome in which induction of ovulation results in a wide spectrum of clinical and laboratory symptoms and signs. At one end of the spectrum, there is only chemical evidence of ovarian hyperstimulation with an increased production of steroids; at the other end of the spectrum are massive ovarian enlargement, ascites, pleural effusion, hemoconcentration, oliguria, electrolyte imbalance, and hypercoagulability, a life-threatening derangement in hemostasis.

Ovarian hyperstimulation syndrome (OHSS) is characterized by massive transudation of protein-rich fluid (mainly albumin) from the vascular space into the peritoneal pleural and to a lesser extent to the pericardial cavities. The intensity of the syndrome is related to the degree of the follicular response in the ovaries to the ovulation-inducing agents. OHSS is still a threat to every patient undergoing ovulation induction

There are two types of severe OHSS:

1. Early which occurs in response to hCG trigger within 5–7 days of ovulation
2. Late which is caused by the rising hCG hormone levels produced by the placenta in conception cycles

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8.2 Classification of OHSS

Schenker and Weinstein [1] divided OHSS into three main categories—mild, moderate, and severe.

8.2.1 Mild Hyperstimulation

Chemical hyperstimulation is a very common accompaniment of ovulation induction. The mild form of OHSS presents a sensation of abdominal heaviness, tension, swelling, and pain. The physical findings are bilateral ovarian enlargement by multiple follicular and corpus luteum cysts; the ovaries may be up to 6 cm in diameter. In recent years mild hyperstimulation has become more common with induction of superovulation in ovulatory women participating in the various kinds of assisted reproduction programs. Occasionally the cyst may rupture or undergo torsion. This often presents a difficult problem in the differential diagnosis between a ruptured cyst, torsion of adnexa, and an ectopic pregnancy.

8.2.2 Moderate Hyperstimulation

In cases of moderate hyperstimulation, the abdominal discomfort is more pronounced. Gastrointestinal symptoms, such as nausea, vomiting, and (less frequently) diarrhea, are present. There is some weight gain and an increase in abdominal circumference. The ovaries are enlarged up to 12 cm in diameter, and some ascitic fluid is detected by ultrasonography.

8.2.3 Severe OHSS

Severe ovarian hyperstimulation syndrome is one of the most important complications of ovarian stimulation with severe morbidity and is still a life threat to every patient undergoing ovarian induction. Despite the fact that only few mortality cases have been reported, we believe that more cases of maternal mortality may exist, which have gone unpublished likely due to malpractice issues. The clinical manifestations may include pleural effusion, pericardial effusion, hypovolemia, impairment of renal function, electrolyte imbalance, disturbance in liver function, thromboembolic phenomena, shock, tension ascites, and adult respiratory distress syndrome (ARDS). The condition of a patient with severe OHSS improves within several days when she is correctly treated and when conception does not occur. The large ovarian cysts gradually subside after the abrupt appearance of clinical symptoms of hyperstimulation. The presence of ascites is a major sign of the capillary leak phenomenon present in OHSS. There is a direct connection between the intensity of capillary permeability and the severity of OHSS, as has been shown in our experimental model [1, 2]. Intraperitoneal pressure exceeds the normal intraluminal pressure of

the abdominal vena cava, the inferior vena cava is compressed, and blood flow in the interior vena cava is reduced. During these pathological changes, there is reduced preload to the heart, leading to decreased cardiac output and impairment of renal and respiratory function.

The most serious complication associated with OHSS is thrombotic phenomena as shown in Schenker and Mor review of 140 cases of OHSS on both arterial and venous side [3]. Thromboembolic events on arterial side were the common cause of death. The mechanism of thromboembolism in the course of ovarian hyperstimulation syndrome mainly the arterial one was explained by us as result of increased permeability of blood vessels in response to excessive vasoactive substances of ovarian origin and vasoconstrictive effects of some other agents of ovarian origin, which lead to hemoconcentration and hypovolemia with resultant arterial hypotension, increasing the risk of OHSS. Hormones play an increased role in both arterial and venous thromboembolism. Gonadotropin administration, increased supraphysiological concentrations of 17β-estradiol following ovulation induction, may be a risk factor especially in patients with inherited thrombophilias [3]. Arterial events are predominantly cerebrovascular accidents, usually occurring concurrently with the onset of OHSS, which could be life threatening, especially when occurring in sites such as cerebral and carotid arteries. Venous thromboses occur several weeks later and are mostly reported in unusual yet specific sites such as large veins of the upper extremities and neck [4, 5]. Prophylactic anticoagulant therapy is indicated to high-risk patients. Prophylaxis should be initiated in patients with thrombophilia and who develop moderate–severe OHSS [3].

Hepatocellular and cholestatic changes have been noted with and without conception. Several factors may account for these changes including increased estrogen levels and increased vascular permeability.

Severe OHSS is characterized by an extraparenchymal restrictive type of pulmonary dysfunction, attributed to intraabdominal or pleural fluid accumulation, which limits descent of the diaphragm and expansion of the thoracic cage. This may induce uncoordinated lung ventilation and atelectasis with subsequent ventilation-perfusion mismatch and hypoxemia. The clinical picture may deteriorate further because of pulmonary infection, pulmonary thromboembolism, or ARDS, all of which have distinct clinical, radiographic, and blood gas characteristics [6].

Hypoalbuminemia, a well-established feature of OHSS, is caused by leakage of albumin to the third space we determined globulin concentrations in the plasma and ascitic fluid of patients with severe OHSS from the time of admission until convalescence. Our studies demonstrated severe OHSS are at increased risk for infection due to leakage of gamma globulins from intravascular space [7].

8.3 Incidence

The incidence and severity of OHSS vary between different types of fertility treatment, with treatments involving greater degrees of ovarian stimulation being associated with a higher incidence. In cycles of In vitro fertilization (IVF), mild OHSS affects around one third of cycles, while the incidence of moderate and severe OHSS ranges from 3.1 to 8% [8].

8.4 Pathogenesis of OHSS

There is a continuous effort to find the exact factors responsible for the increased vascular permeability which was shown in our experimental model: such as histamine, serotonin, prostaglandins, prolactin, and variety of other substances that were implicated in the past. However, only scant data support an important role for any of these factors.

The following factors were studied:

Histamine—It was found in animal model that ovarian hyperstimulation syndrome could be blocked in rabbits by administration of antihistaminic preparations. In animals treated with antihistamine, a more rapid regression of the hyperstimulated ovaries was observed than in a control group. Although these animal studies had promising results, later studies demonstrated no difference in histamine levels between rabbits, in whom OHSS was induced, and controls [9].

Estrogens—Abnormally high levels of various steroids, estrogens in particular, are found in ascitic fluid and serum in cases of OHSS following hMG-hCG ovulation induction. Thus, it is not a surprise that estrogens were implicated as a possible triggering factor that eventually increases capillary permeability. On the other hand, it is known that the administration of high doses of estrogens do not, by themselves, produce clinical hyperstimulation. Moreover, Meirow et al. [10] concluded that estradiol measurements alone are not sufficient to alert the physician to the possible development of OHSS.

Prostaglandins—Experiments in animal models set out to determine whether prostaglandins are the "active substances" playing a role in the development of this syndrome. It was demonstrated in early experiments on an animal model that indomethacin, a blocker of prostaglandin synthesis, can prevent the fluid shift associated with the ascites, pleural effusion, and hypovolemia seen in this syndrome [2]. Moreover, other animal studies showed that in the presence of OHSS, ascites formation is not effectively suppressed by indomethacin, and, in the clinical setting, indomethacin was used as a therapeutic measure in cases of severe OHSS with variable results. Therefore, the role of prostaglandins in triggering the pathological processes of OHSS was not proved.

Renin–angiotensin system—Increased vascularity as well as increased capillary permeability at the time of ovulation is an important part of the angiogenic response in the follicle. The angiogenic properties of human follicular fluid combined with high plasma renin-like activity, angiotensin II-like immunoreactivity, and angiotensin-converting enzyme (ACE) raised the hypothesis on the possible involvement of renin–angiotensin system in the pathogenesis of OHSS through new vessel formation and increased capillary permeability. The involvement of a locally activated renin–angiotensin–aldosterone cascade has been implicated as a possible cause of the severe form of the syndrome through neovascularization and increased capillary permeability rate through endothelial cells in vitro. We studied plasma renin activity and aldosterone in patients with ovarian hyperstimulation and demonstrated: the pattern of plasma renin activity in hMG hyperstimulated cycles is characterized by a mid-luteal peak which declines to normal in the late luteal phase in non-conceptual cycles, whereas a sustained elevation of plasma renin activity occurs in

conceptual cycles. A direct correlation between the magnitude of plasma renin activity and the severity of OHSS was established [11].

According to this concept, the increased capillary permeability present in OHSS is due to the involvement of the renin–angiotensin system and the synthesis of prostaglandins in the ovaries. However, although the renin–angiotensin system may explain some of the characteristics in OHSS such as vasoconstriction as well as several other signs, it is not clear whether this system triggers the cascade leading to OHSS or merely is a secondary reactional feature.

Vascular endothelial growth factor—It was found by us and others that VEGF is responsible for the significant increase in the capillary permeability in OHSS [12]. VEGF, also known as vascular permeability factor (VPF), can provoke extravascular fluid accumulation, hemoconcentration, and elevated plasma concentration of von Willebrand factor, all known complications of OHSS. VEGF is a potent vasoactive protein with a remarkable permeability enhancing capacity that is approximately 1000 times that of histamine. Elevated levels of VEGF were found in the serum of patients who developed severe OHSS. Follicular fluid VEGF was found to be 100-fold greater than serum or peritoneal fluid 36 h after hCG administration.

Abramov et al. [12] investigated the role of VEGF in OHSS. Samples of therapeutic paracentesis were collected from severe OHSS patients. They found that VEGF is the major capillary permeability factor in OHSS ascites, since adding specific antibodies against VEGF (rhVEGF) was able to neutralize 70% of capillary permeability activity. Several other evidence for the key role of VEGF in the pathogenesis of OHSS was also found. High concentration of this substance was found in ascites from OHSS patients. Lately, dynamic changes of VEGF levels in the ascitic fluid of patients with severe OHSS were reported [12]. Moreover, it was found that VEGF is HCG trigger for OHHS.

8.5 Human Chorionic Gonadotropin

Severe OHSS is depended on either exogenous administration of hCG or endogenous pregnancy-derived hCG. It is administered during ovarian stimulation for both triggering ovulation and for luteal support. It is well known that hCG administration is critical for the development of OHSS. This iatrogenic syndrome cannot be totally prevented by GnRH substitution for hCG and inducing endogenous LH surge.

8.6 Treatment

Mild OHSS usually does not require any active form of therapy other than observation and maintenance of hydration by the oral route. Moderate-grade OHSS requires close observation and, in most instances, hospitalization, since patients may rapidly undergo a change of status, particularly when conception occurs, and it may become severe with subsequent complications; thus, vigilant observation is required. Patients with severe OHSS require immediate hospitalization and treatment.

During hospitalization, meticulous monitoring of hemodynamic stability is required by restoration of the depleted intravascular volume. Large-volume crystalloid infusion is recommended. However, these patients must be closely monitored, as this can result in sequestration of fluid in the third space. Since no treatable single causative mechanism has been found for this syndrome, therapy has remained conservative and supportive, aimed at refilling the arteriolar vasculature, mobilizing fluids from the third space back to the intravascular tree, maintaining circulatory hemodynamics, and preventing hemoconcentration. A rare but life-threatening risk for patients with severe hypovolemia involves arterial venous thromboembolism; therefore, prophylactic anticoagulation is warranted in cases of severe OHSS from the time of diagnosis through the first trimester of pregnancy [13].

We have previously shown that severe OHSS is characterized by leakage of albumin (with a molecular weight of 69 kDa) as well as IgG and IgA (with molecular weights of 150 and 180 kDa, respectively) to the abdominal cavity. Since IgM, which has a molecular weight of approximately 900 kDa, did not leak at all and since IgA leaked much less than IgG and albumin, we suggested that molecular human albumin, however, is considered the most "physiologic" solution for this purpose and is probably the most common one used. Its popularity may be attributed to publications that reported a benefit of prophylactic administration of human albumin before and immediately after oocyte retrieval in women at high risk for severe OHSS. However, some recent reports could not reproduce these results and found no significant benefit of human albumin therapy in prevention of severe OHSS.

We compared human albumin with 6% hydroxyethyl starch, a powerful, high-molecular-weight colloid currently used to treat other states of intravascular volume depletion, such as burns and hemorrhagic or septic shock. It was proved that 6% hydroxyethyl starch has advantage over albumin [14].

Tension ascites with oliguria calls for paracentesis. Impending renal failure and unrelenting hemoconcentration require intensive care and possibly dopamine drip. Heparin should be added for thromboembolic phenomena, whereas surgical intervention should be reserved for ovarian torsion, rupture of cysts, or ectopic (heterotopic) gestation. Therapeutic termination of an existing pregnancy may be lifesaving when all other measures have failed, making both patient and physician face extremely difficult decision with vast psychological consequences for the patient.

The majority of studies examining the treatment of OHSS are retrospective cohort studies that mostly evaluated both volume expanders and surgical interventions. There are more robust data supporting surgical intervention, such as paracentesis and culdocentesis, than fluid management [13].

8.7 Prevention

The key to the primary prevention of OHSS during ovarian stimulation is individual approach recognizing risk of the patient to develop OHHS. Several measures can he employed to prevent OHSS [15]. There are, however, numerous reasons why even

with the most careful and painstaking preventative measures, OHSS cannot be eliminated.

Monitoring of induction of ovulation is the most reliable method in the prevention of OHSS. Measurable parameters, which more or less accurately reflect follicular maturation, are used to monitor ovulation induction since direct observation is impossible.

Clinical evaluation is important, and such methods as cervical scoring may he used as adjuvant methods of evaluation. Determining the cervical score reflects indirectly the total estrogen activity.

Serum estrogen values have established their effectiveness in monitoring induction of ovulation.

Estrogen monitoring has effectively reduced OHSS with clinical symptoms necessitating hospitalization [4]. Higher levels of 17 B-estradiol are reached in induced cycles to achieve the optimal pregnancy rate. However, we and others have observed OHSS with peak plasma estradiol levels of >2000 pg/mL, HCG should be withheld then.

An additional factor that may serve as a warning sign is the slope of rise of the plasma estradiol level. If values are more than doubling during 2 or 3 days (steep slope), then this should be regarded as a serious warning sign and HCG withheld in that cycle. In assisted reproductive programmers, HCG should be withheld when estradiol levels are >3000 pg/mL.

We, along with others, have demonstrated that there is a linear correlation between the follicular diameter and estradiol levels in plasma in normal ovulatory cycles. However in induced cycles, where there is more than one dominant follicle and several maturing follicles, there is a poor statistical correlation between the ultrasonographic ovarian morphology and the plasma estradiol level.

In assisted reproductive of ovarian stimulation, the following manipulations and interventions during the treatment cycle have been used:

(a) Withholding HCG—canceling of cycle—As OHSS is associated with hCG, terminating the ovulation cycle by canceling the hCG trigger in the presence of several risk factors for OHSS is the most effective technique to prevent OHSS. hCG induces the production of VEGF, the primary mediator of OHSS. It is usually reserved for patients at high risk of OHSS and those with total loss of cycle control. Canceling a cycle has an economic and psychological effect on the patient.
(b) Rescue of overstimulated cycles—coasting—Withholding exogenous gonadotropins and postponing the hCG trigger until a patient's E2 level has declined. Coasting leads to the selective regression of the pool of immature follicles, thereby reducing the functioning granulosa cell mass available for luteinization and resulting in a decline in vasoactive substances involved in the pathogenesis of OHSS, including VEGF. Coasting has been shown to reduce the incidence of OHSS in high-risk patients but affecting cycle outcome. Coasting results in lower pregnancy rates.

(c) Aspiration of follicles—Has a protective effect with a decline in hormonal levels being noted. This may account for the reduced incidence of OHSS, but this approach does not offer complete protection against the development of OHSS.
(d) Albumin—Potential benefit of intravenous (IV) albumin at the time of oocyte retrieval to prevent OHSS was reported. An early Cochrane review clearly showed a benefit associated with the administration of IV albumin at the time of oocyte retrieval in patients at high risk of OHSS, with no effect on pregnancy rate. Recent studies found that while there was no statistical benefit regarding the rate of OHSS, it may reduce pregnancy rates [12].
(e) Dopamine agonist—A therapeutic strategy to prevent OHSS development is to use a dopamine agonist in order to benefit from its established action of inhibiting phosphorylation of VEGFR2 and preventing increased vascular permeability. It reduces the early onset of OHSS, without causing any effect in pregnancy, implantation, and miscarriage rate [16].
(f) GnRH agonist triggering—GnRHa triggering minimizes the risk of OHSS and secures the appropriate maturation of oocytes. The GnRHa triggering is possible only when using a GnRH antagonist protocol and requires modified luteal support in order to be as efficient as hCG triggering. The complete eradication of OHSS has made the GnRHa triggering concept the protocol of choice in IVF with fresh embryo transfer. It was demonstrated that if luteal support is with intramuscular progesterone and estradiol patches, the delivery rate is comparable to that seen after hCG triggering [17].
(g) Freezing all the oocytes or embryos—Since pregnancy will increase the severity of OHSS, it is often prudent to postpone embryo transfer to a subsequent cycle in patients that are at high risk for OHSS.
(h) Aspirin-platelet cyclooxygenase-1 (COX-1) inhibitor—There is fair evidence that it reduces OHSS: A large RCT included initiation of 3154 IVF cycles, for which gonadotropin-releasing hormone agonist was used in 2425 cycles, 1503 cycles randomly selected for low-dose aspirin treatment starting from the first day of controlled ovarian hyperstimulation compared with no treatment in the remaining 922 cycles [18]. Result showed only two (0.25%) cases of severe or critical OHSS developing in the 780 high-risk patients treated with 100 mg aspirin, as compared to 43 patients (8.4%) of the 412 who did not receive aspirin; there was no difference in pregnancy outcomes in the two groups [19].
(i) Metformin—The use of this insulin-sensitizing agent increased clinical pregnancy rates and decreased the risk of OHSS in PCOS patients [18]. By improving intraovarian hyperandrogenism, it is theorized that metformin can affect the ovarian response by reducing the number of non-periovulatory follicles and thereby reduce estradiol secretion. A recent meta-analysis that included 12 studies (1516 participants) showed no significant differences between metformin and placebo groups for rates of pregnancy (risk ratio [RR] 1.11, 95% CI 0.92–1.33), live birth (RR 1.12, 0.92–1.36), spontaneous abortion (RR 1.00, 0.60–1.67), or multiple pregnancy (RR 0.96, 0.47–1.96). However, OHSS rate was significantly lower among patients who received metformin than among

those who received placebo (RR 0.44, 0.26–0.77). Regarding the use of metformin in lean PCOS patients, some studies show that it does not decrease the risk of OHSS.

(j) Calcium—Increasing calcium levels has an inhibitory role on adenylyl cyclase resulting in cAMP inhibition and thus renin inhibition as well, which lowers VEGF production and thus lowers the risk of OHSS. Administration of 10 mL of 10% calcium gluconate on the day of the oocyte retrieval and days 1, 2, and 3 after oocyte retrieval associated with a reduction on moderate and severe OHSS without compromising the pregnancy rate [18].

(k) Luteal support phase—Progesterone appears to provide the best method of providing luteal phase support, as it is associated with higher rates of live birth or ongoing pregnancy than placebo and lower rates of OHSS than hCG. According to a meta-analysis of 94 RCTs, there was no evidence of a difference between progesterone and hCG regimens (hCG regimens included hCG alone and hCG with progesterone) in live birth or ongoing pregnancy rates (OR 0.95, 95% CI 0.65–1.38, 5 RCTs, 833 women, I2 = 0%, low-quality evidence). Progesterone was associated with lower OHSS rates than hCG regimens (OR 0.46, 95% CI 0.30–0.71, 5 RCTs, 1293 women, I2 = 48%) [18].

Conclusions

OHSS is characterized by massive transudation of protein-rich fluid (mainly albumin) from the vascular space into the peritoneal pleural and to a lesser extent to the pericardial cavities. The intensity of the syndrome is related to the degree of the follicular response in the ovaries to the ovulation-inducing agents. Ovarian hyperstimulation syndrome is still a threat to every patient undergoing ovulation induction. The pathophysiology of ovarian hyperstimulation syndrome is of extreme importance in the face of the increased use of ovulation induction agents as well as the development of sophisticated assisted reproductive techniques. In this manuscript we reviewed the factors that are probably responsible for this syndrome. The correlation found between plasma cytokine activities and the severity of OHSS suggests that plasma cytokines may be involved in the pathogenesis of OHSS and may serve as a mean for monitoring the syndrome during the acute phase and throughout convalescence. The interactions between cytokine and non-cytokine mediators of the syndrome, such as the renin-angiotensin system and vascular endothelial growth factor (VEGF), await further clarification. However, it seems that a combination of immune and nonimmune mechanisms may allow profound understanding of this enigmatic disorder.

VEGF, endothelin-1, renin-angiotensin system, and cytokines probably play a pivotal role in the increased capillary permeability which explains most of the symptoms and signs of OHSS; however the puzzle is not complete, and many questions are still open. Awareness of possible mechanisms and factors in the pathophysiology of OHSS will hopefully provide opportunities to design specific treatment regimens effective for both prevention and treatment of this potentially fatal iatrogenic condition.

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