Ovarian Hyperstimulation Syndrome

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I. INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic side effect associated with assisted reproductive technology. The disorder is defined by enlargement of cysts in the ovaries, as well as fluid movement from the intravascular space to the third space due to an increase in capillary permeability as well as ovarian neoangiogenesis. The cause of the condition is being treated with human gonadotrophin chorionic (hCG). OHSS is very rare without the use of hCG. Its effect on the overall wellbeing of patients may be extremely detrimental and even tragic cases have been documented. The link with hCG OHSS is believed to be controlled by an increase in the expression of the angiogenic molecules VEGF. The frequency in moderate OHSS is thought to range somewhere between 3 to 6 percent, however the more severe form could be seen in 0.1-3 percent of cycles. OHSS is recognized in two different forms: The initial type that is OHSS, (within days after the ovulation-triggering injection of HCG) however, despite being triggered by hCG is linked to an overexaggerated response of the ovarian to gonadotrophin stimulation. On the other hand, the latter type (10 days following the injection of hCG)(after 10 days after hCG) 1 2] is linked to the secretion of the placental hCG.

II. PATHOPHYSIOLOGY

The underlying cause of OHSS is not known, however it is thought to be related to increased vascular permeability in area surrounding the ovaries as well as their vasculature. 3 3The key is an equilibrium of proangiogenic and antiangiogenic elements present in the follicular fluid. B-hCG and its derivatives estrogen, estradiol prostaglandins, prolactin and histamine are all involved in OHSS however, it is becoming increasingly clear that vasoactive substances like interleukins, tumor necrosis factor (TNF)-a endothelin-1, and VEGF produced by the ovaries are associated with increasing the permeability of vascular blood vessels. [4]

III. PRIMARY RISK FACTORS

Factors that are likely to increase responses to stimulation of the ovary comprise an early age and a history of an elevated response to gonadotrophins, prior OHSS or polycystic Ovarian Syndrome (PCOS). [5]

IV. SECONDARY RISK FACTORS

Numerous Ovarian response parameters have been examined to determine their ability to determine the progression of OHSS and [6] which include absolute levels, or the rate of rise in Follicular volume, serum E2, the number and size of oocytes that have been collected.

V. CLINICAL FEATURES

- Abdominal pain, nausea , and vomiting
- Ascites and tension
- Peritonitis, whether generalized or localized.
- Acute abdominal pain
- Hypotension or hypovolemia
- Dyspnea
- Hypercoaguable state
- Electrolyte imbalance
- Acute renal failure

VI. CLASSIFICATION

Grades of OHSS are as follows [2]:
Mild OHSS

- Grade 1: Abdominal Distention, and discomfort
- Grade 2: Grade 1 Disease with nausea, vomiting or diarrhea, and/or the ovarian enlargement ranging from 5 to 12 cm. Moderate OHSS
- Grade 3 - Characteristics of moderate OHSS and the ultrasonographic proof of ascites

Severe OHSS

- Grade 4 - Symptoms of moderate OHSS, plus evidence of ascites or breathing difficulties and hydrothorax.
- Grade 5-All of these, plus an increase in blood volume, an increase in blood viscosity as a result of hemoconcentration, coagulation issues as well as a decrease in renal perfusion function.

VII. PREVENTIVE MEASURES:PRIMARY PREVENTION

Reducing exposure to gonadotrophins

A. Cycle cancellation
B. Coasting ("Soft landing") when high risk patients show an increase in (>3000 pg/mL) serum levels of estradiol

and high numbers (>20 per Ovary) of follicles stimulated gonadotrophin therapy, it can be reduced or stopped maintaining GnRH antagonist administration.

C. Modification of the trigger for ovulation agent: Even though reliable information aren't available, it's possible that doses of hCG less than 10,000 or 5000 IU typically used could trigger adequate maturation of oocytes and reduce the risk of OHSS. Replacing hCG with either endogenous or exogenous LH as an ovulation trigger can significantly impact the risk of developing early forms of OHSS. Endogenous LH surge may be caused through the administration of a quick-acting GnRH antagonist. This can only be achieved in the absence of pituitary desensitization caused through the GnRH antagonist. Combination with antagonists remains possible.
D. Administration of macromolecules Albumin administration. Administration of albumin on a regular basis can disrupt the progression of OHSS through increasing the plasma pressure oncotic and binding mediators from ovarian origin.
E. All embryos can be frozen for cryopreservation: Instead of cancelling the cycle, it's also possible to inject HCG to reclaim the ocytes as well as freeze the embryos.
F. GnRH antagonists - GnRH antagonists (GnRHa) are linked to an increased prevalence of OHSS. [7]
G. The avoidance of hCG is for the support of the luteal phase
H. in vitro maturation

For patients who are at a high risk for developing OHSS, in vitro maturation (IVM) of oocytes provides the potential to be a powerful tool to aid in OHSS prevention. Although it has many advantages for safety, IVM is not yet widespread due to the lower rate of live births as compared to conventional IVF. However, the clinical outcomes have been improving in recent years, and pregnancies of between 20 and 54 percentage have been recorded. [8]

I. Dopamine agonist administration

Cabergoline blocks VEGF receptor 2 phosphorylation level and the vascular permeability that is associated with it, but without affecting luteal angiogenesis . This reduces its incidence 'early'(within nine days following hCG) time of onset of OHSS. Although cabergoline is not used however, the OHSS prevalence could be up to 10.8%[9]

J. Nonsteroidal anti-inflammatory administration

A large-scale RCT showed that low-dose aspirin is linked to a reduction in OHSS prevalence (0.25 percent vs.8.4 percent) in a high-risk population with comparable pregnancy rates. 10. Meloxican could reduce in the OHSS and ovarian burden as well as the expression of VEGF in a model animal. [11]

Treatment based on degree of hyperstimulation

Mild hyperstimulation

The treatment for OHSS is to be supportive, if needed. The mild ovarian hyperstimulation could develop into severe or moderate illness particularly if there is a chance of conception. So, women suffering from mild diseases should be watched for an increase in abdominal size and weight gain that is sudden and abdominal pain in a ambulatory manner for at least two months or till menstrual bleeding is observed.

Moderate hyperstimulation

Treatment for moderate OHSS is based on observation, rest and providing adequate fluids and sonographic examination of the sizes of cysts. Concentrations of electrolytes in serum, hematocrits , and creatinine levels must also be examined.

A lower intake or output than 1000 mL/d, or a difference in fluid balance that is greater than 1000 mL/d are an indication of concern. The first sign of resolution for OHSS is evident when the cysts shrinkas shown in two consecutive ultrasonographic studies and when the clinical signs disappear. However, the early detection of progress to the severe version of the disorder is characterized by a constant weight increase (>2 pounds/day) or a rise in the severity of symptoms that are already present or the appearance of new signs (eg diarrhea, vomiting and dyspnea). [13]

Severe hyperstimulation

Severe OHSS isn't often seen, but it can be risky. The severe and critical types of OHSS can be fatal as well as a history-taking and physical examinations are essential in the moment of admission. In the majority of clinical scenarios patients need to rest on their beds. Every day physical examination should include measuring the patient's weight as well as abdominal girth. The fluid balance should be evaluated every four hours.

Treatment of hyperstimulation that is severe is aimed at maintaining blood volume in the intravascular. In parallel, the aim is to restore the shaky electrolyte and fluid balance, reducing the secondary effects of ascites as well as hydrothorax, and preventing thromboembolic complications.

The most important treatments are for fluid management and the correction of hypovolemia. The first step is rapid infusion of intravenous normal Saline. Dextrose 5percent in normal saline, or normal Saline is infused at an amount of between 125 and 150 mL/h. This is followed by four hour tabulations for urine output. If the production of urine improves or is restored the maintenance program is implemented. The patient is examined for any clinical symptoms of excessive hydration. If urine output is not satisfactory Hyperosmolar intravenous therapy may be suggested by the infusion of 200mL of human albumin at 25. Diuretics are used for patients suffering from low production of urine and hypovolemia is ineffective and potentially dangerous. [13]

To avoid thrombosis Heparin ranging from 5000-7500 U/day is administered on the day of admission. The dose is removed after sufficient mobilization has been completed.

To manage ascites, ultrasonographic-guided paracentesis is indicated if the patient has severe discomfort or pain or if she has pulmonary or renal compromise.

Critical hyperstimulation

Critical OHSS could be caused by renal failure, hepatic damage, thromboembolic phenomenon, ARDS and multiorgan failure. Management and treatment is a need for the most intensive care in a critical care unit.

Resolution

After a few days, the third-space fluid is beginning to return to the intravascular space. Hemoconcentration decreases, and natural diuresis occurs. The intravenous fluids are tapered when

the amount of oral fluid consumed by the patient increases. A complete resolution usually takes between 10 and 14 days after the onset of the initial symptoms.

Surgical care

OHSS tends to self-limit the illness. Thus, treatment should be limited and targeted to the symptoms. Medical therapy is sufficient for the majority of patients. Women suffering from severe symptoms typically require medical treatment that is intensive. Surgery is required only in the most extreme circumstances like the event of tear-up in the cyst, an ovarian tumor and/or internal hemorrhage.

Prognosis

The outlook is favorable when OHSS is moderate or mild. In cases of severe OHSS the prognosis can be positive if proper treatment is offered.

VIII. RECOMMENDATIONS

- If gonadotrophin stimulation to induce an ovulation-inducing effect is necessary it is recommended to use "friendly" stimulation protocols aimed at (SOFT) one Ovarian Follicles. low-dose step-up routine and step-down regimens, the using antagonists, and using blood as well as sonographic monitoring of the the ovarian response.
- The ovulation trigger hCG should be replaced by more secure methods such as rLH or endogenous GnRH-surge with an antagonist.
- In IVF/ICSI, the concept of getting as many oocytes as is possible should be replaced with gentler stimulation strategies aiming at less Oocytes that are of high quality.
- In the event of a risk, patients should be aware of the possibilities including cancelling, coasting or freezing embryos to be used for replacement later on.
- When symptoms of OHSS are observed patients must be informed in a timely manner and hospitalization must be considered when there is a slight improvement.
- The patients require an ward in a hospital in which there is a clinical image recognized and the staff has the expertise to treat and follow-up. Admission to an intensive-care unit is required in the event that critical OHSS is observed.
- The recording of every case of severe OHSS and their results must be made mandatory for all ART programs. It should be mandatory following every ovulation induction.

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