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DEBATE

OHSS-free IVF practice: Dream or reality

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1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening complication of controlled ovarian stimulation (COS). OHSS is an iatrogenic complication of ovulation induction, which may cause serious impact on patient's health. OHSS is the most feared complication of IVF-related ovarian stimulation, which in its severe form leads to hospitalization and in the worst case scenario fatal complications (1).

2. Incidence

There is no universal consensus on the exact incidence of OHSS. The incidence of OHSS varies between treatment and patient groups and accurate estimates from the literature are difficult owing to the variety of classification schemes used. OHSS is classified according to its severity into: mild, moderate, severe, and critical. It is also classified into early and late according to the onset of its development. Early onset OHSS is self-limited in case no pregnancy occurs. Late onset OHSS develops ten days or more after ovum pick up and is poorly correlated to ovarian response after stimulation.

As many as 33% of IVF cycles have been reported to be associated with mild forms of OHSS (2). While these are often described as not being clinically significant, the severity of OHSS can worsen over time. The incidence of moderate OHSS is estimated to be between 3% and 6%, while the severe form may occur in 0.1–3% of all cycles (3). Among high risk women the incidence approaches 20% (4).

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3. Pathophysiology

Development of multiple follicles forms the basis of OHSS. Exogenous hCG administration for the final maturation of oocytes or endogenous production of hCG after pregnancy is the second factor needed for the development of severe OHSS (1).

The underlying cause of OHSS is not known, but the release of a vasoactive ovarian factor is likely to be involved. Increased capillary permeability and ovarian enlargement are the principal characteristics of OHSS. Fluid escapes from vessels into the third space, resulting in hypovolemia. Severe OHSS is characterized by massive ovarian enlargement, pleural effusion, ascites, oliguria, hemoconcentration, and thromboembolic phenomena.

Prevention of OHSS by whatever means would be our goal to achieve our dream of OHSS-free IVF practice. However, mild and moderate OHSS have minor medical sequelae. Therefore, our discussion will be on how to prevent or lower the incidence and severity of severe OHSS.

The following strategies will be discussed in brief:

1. Identification of patients at risk of OHSS.
2. Withholding or reducing the dose of hCG.
3. GnRH antagonist protocols.
4. GnRH agonists to trigger final oocyte maturation.
5. Dopamine agonist administration.
6. Coasting (withholding gonadotrophins).
7. Intra-venous fluid administration.
8. In vitro maturation of oocytes (IVM).
9. Cryopreservation of embryos.

3.1. Identification of patients at risk of OHSS

Women at higher risk of developing OHSS include those with polycystic ovaries (necklace sign), women under 30 years of age, use of GnRH agonists, and previous episodes of OHSS. Other women at risk are identified during or after gonadotrophin stimulation. Those who develop multiple follicles during stimulation, those who have high serum estradiol > 4000 pg/ml, conception cycles, exposure to LH/hCG, and hCG luteal supplementation. Different strategies for preventing OHSS have been proposed, to identify women at risk. As this is not always possible, there are several options to avoid the development of the full blown syndrome.

3.2. HCG withholding or reducing hCG dosage

OHSS could be theoretically eliminated if hCG is not used, since no moderate or severe forms of OHSS were observed without the administration of this hormone. There is enough evidence to support that hCG is the main triggering cause of OHSS. So withholding hCG administration is a safe alternative to avoid OHSS, postponing the treatment cycle till the ovaries have been rendered quiescent (5). Cycle cancellation has financial and emotional implications, frustrates both patient and physician.

Concerning ovulation induction, the historical dosage of hCG is 10,000 IU. Two recent studies showed that reducing hCG dose to 3300 and 2500 IU, respectively did not worsen IVF results. In addition, no moderate or severe OHSS was observed. Therefore, adopting the policy of reducing hCG does not worsen IVF results and may reduce the incidence of severe OHSS (6,7).

3.3. GnRH antagonist protocols

GnRh antagonist, directly and rapidly, inhibits gonadotrophin release within several hours through competitive binding to pituitary GnRH receptors. They are used after exogenous stimulation has begun and can be used to prevent an LH surge during COS without the hypo-oestrogenic side effects, flare-up, or long down-regulation period associated with the GnRH agonists.

The use of antagonists compared with long GnRH agonist protocols was associated, in a recent meta-analysis, with a large reduction in OHSS and there was no evidence of difference in live birth rates (8).

3.4. GnRH agonists to trigger final oocyte maturation

GnRH agonists have been used to trigger final oocyte maturation as an alternative to hCG to prevent premature LH surge (9). They can, also, be used to induce oocyte maturation instead of hCG during a GnRH antagonist protocol. Replacing hCG with GnRG agonist was shown to be financially acceptable, with good pregnancy rates and a dramatic decrease in moderate and severe OHSS (10,11). However, GnRH agonists can be only used in GnRh antagonist protocols. In addition, a case of severe early onset OHSS after GnRH agonist triggering has been recently reported (12).

3.5. Dopamine agonist administration

Recently, dopamine agonists were proposed as a prophylactic treatment for OHSS in women at high risk in IVF/ICSI treatment cycles. The dopamine agonist, cabergoline, inhibits partially the VEGF receptor 2 phosphorylation and associated vascular permeability without affecting luteal angiogenesis. In the most recent systematic review and meta-analysis, it was shown that prophylactic treatment with the dopamine agonist, cabergoline, reduces the incidence but not the severity of OHSS without compromising pregnancy outcomes (13).

3.6. Coasting (withholding gonadotrophins)

Coasting is a strategy in which the administration of hCG is postponed in women who respond to ovarian stimulation with high plasma levels of estradiol until the patient has achieved an estradiol level considered to be safe (14). Coasting is a part of the step down approach of ovulation induction in order to select a reasonable number of mature follicles without the risk of OHSS. Early reports showed beneficial effect of coasting in reducing but not eliminating the risk of severe OHSS. The reason for OHSS prevention by coasting remains controversial. Increased rate of apoptosis in ovarian follicles, in particular those less than 14 mm, is the most possible explanation for the effects of coasting. In a recent Cochrane systematic review, there was no evidence to suggest a benefit of using coasting to prevent OHSS compared with no coasting or other interventions (15). There was no difference in the incidence of moderate and severe OHSS, live birth or in the clinical pregnancy rate between the groups (15). Significant fewer oocytes were retrieved in coasting groups compared with GnRh agonists or no coasting (15).

3.7. Intra-venous fluids

3.7.1. Albumin

Albumin is a low molecular weight compound with a major impact on oncotic pressure. Human albumin infusion immediately after oocyte retrieval was proposed for the prevention of severe OHSS in high risk patients. However, in the most recent Cochrane systematic review, there was limited evidence of benefit from intravenous albumin administration at the time of oocyte retrieval in the prevention or reduction of the incidence of severe OHSS in high risk women undergoing IVF or ICSI treatment cycles (16).

3.7.2. Hydroxyethyl Starch (HES)

Hydroxyethyl starch (HES) is a plasma expander which has been assayed in the prevention of severe OHSS. Koenig et al. reported a prospective randomized trial in which 6% HES significantly reduced the incidence of moderate to severe OHSS in patients undergoing IVF treatment (17). HES was shown, in a recent meta-analysis, to markedly decrease the incidence of severe OHSS (16).

3.8. In vitro maturation (IVM) of oocytes

In vitro maturation of oocytes (IVM) is a relatively new technique used recently to prevent OHSS. The only reliable way to eliminate the risk of OHSS is complete avoidance of gonadotrophin stimulation. During an IVM cycle, immature oocytes are retrieved with minimal or no ovarian stimulation, then cultured for a variable period of time before being fertilized in vitro or by ICSI. The use of IVM can result in clinical pregnancy rates that compare to those obtained with conventional IVF (18). The obstetric and perinatal outcomes of IVM pregnancies are similar to those conceived from standard IVF conceptions (18). IVM may not replace conventional IVF due to difficulties encountered in retrieving immature oocytes from unstimulated ovaries and in their culture. One report showed a higher rate of meiotic spindle and chromosomal abnormalities from immature oocytes (19). However, a more recent report showed that more than a thousand healthy infants have been born by IVM without an increase in fetal abnormalities (18). IVM may play an increasingly significant role in assisted

reproduction, in particular, in centers that manage a good percentage of high responders and patients at increased risk of OHSS.

3.9. Cryopreservation of embryos

As OHSS is more common in conception cycles, due to endogenous hCG from the trophoblast of the implanting embryo, elective cryopreservation of all embryos has been postulated. Some units adopt an active policy of freezing all embryos if the patient is deemed clinically to be at high risk of developing OHSS (20). With appropriate counselling, the patient will not regard a total freeze as a failure, but rather as a preventive measure ensuring her health. Importantly, with a good cryo-program, her chances of obtaining a pregnancy will not be reduced (21). In a recent report, there was no statistically significant difference between fresh and frozen embryo transfer pregnancy rates (20). An elective embryo freezing policy to moderate the severity and duration of OHSS does not compromise outcome for women at risk of OHSS (20).

4. Conclusion

OHSS still remains the most ominous complication of COS in IVF/ICSI treatment cycles. Until now, no single unit declared the dream of OHSS-free practice. The most promising approaches to reduce the incidence and severity of OHSS include: identification of patients at risk, GnRH antagonist protocols, triggering final oocyte maturation by GnRH agonist, reducing the dose of hCG, IVM, and cryopreservation of embryos.

I think there is still a long way to go to achieve our dream of OHSS-free practice. We need more patients to be enrolled in large RCT for the above mentioned approaches to identify how feasible it is to completely eliminate the serious complication of OHSS.

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