DEBATE

Ovarian hyperstimulation syndrome: are preventive measures effective?

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INTRODUCTION

Infertility treatment has been changed dramatically over the last decades with the introduction of the new assisted reproduction techniques (ART). Ovarian stimulation, either to induce ovulation in the management of anovulatory infertility or for controlled ovarian hyperstimulation in the course of in vitro fertilization, is a main part of the various ART. Nevertheless, ovarian stimulation entails the risk for the development of ovarian hyperstimulation syndrome (OHSS), the commonest complication as such. Hence, it is of great importance not only to know how to effectively induce ovulation but also how to prevent this severe potential risk.

Ovarian hyperstimulation syndrome is a well-known and important complication of ovulatory drugs. Its development has been described following ovulation induction with almost every drug used for ovarian stimulation, either in the management of anovulatory infertility or during controlled ovarian hyperstimulation for in-vitro fertilization, having an incidence of 0.5-2% (1). The employment of gonadotropin releasing hormone-agonists (GnRH-a) seems to be associated with an increased incidence of OHSS (2-4).

PATHOPHYSIOLOGY

The effective preventive strategy of OHSS presumes updated knowledge of the relevant pathophysiology. OHSS is characterized by a wide spectrum of clinical and laboratory manifestations, including multicystic ovarian enlargement, massive extra-vascular fluid accumulation (peritoneal, pleural or pericardial cavity), combined with intravascular volume depletion, hemoconcentration and electrolytic disturbances (1). Rare but life-threatening complications following the severe forms of OHSS have been reported, such as thromboembolic phenomena, hypovolemic shock, liver dysfunction, renal failure and adult respiratory distress syndrome (5).

The factor(s) causing this phenomenon is until now, not fully elucidated. The main pathophysiological change responsible for OHSS development is thought to be an acute increase in vascular permeability (1), although arteriolar vasodilation (6) was also suggested. Several substances involved in ovarian physiology have been proposed as possible candidates. Initially, estrogens, histamine and prostaglandins were thought to cause OHSS (1). The ovarian renin-angiotensin system was then proposed as the most possible mediator of OHSS (7, 8, 9), but more recently, the vascular endothelial growth factor (VEGF) as well as cytokines, were proposed as protagonists in OHSS pathogenesis (7, 8, 10). Nevertheless, whatever the responsible factor is, it seems that human chorionic gonadotropin (HCG), exogenously administered or endogenously produced, play a key role in the development and
clinical manifestation of OHSS (1).

PREVENTION OF OHSS

While no authentic aetiologic therapeutic methods are currently available, only supportive treatment strategies have been suggested and therefore prevention of the syndrome is paramount.

a) Identification of the main risk factors

The identification of the possible risk factors has always been the key in the prevention of the syndrome. It seems that patients with severe forms of OHSS tend to be younger, while the effect of body weight and body mass index is controversial (11,12). The main predisposing factor for OHSS development appears to be the polycystic ovarian syndrome (PCOS) or solely the polycystic ovaries (13, 14). Hyperandrogenism, PCOS-related or not, constitutes an independent risk factor, whereas increased ovarian volume (>10cc) and the "necklace" sign, a common ultrasound finding in the ovaries of PCOS patients, is eventually linked with OHSS when present even in normoovulatory women (12). Moreover, patients with ovarian hypersensitivity to stimulation and high estradiol (E2) levels on the day of HCG administration tend to develop more frequently OHSS. In addition, the presence of large number of immature and intermediate follicles during ovulation induction and a large number of oocytes retrieved, are predictive of OHSS manifestation and severity (13). A specific combination of parameters (E2>6000pg/ml plus >30 oocytes retrieved) gave an 80% chance of developing severe OHSS (26).

b) Preventive measures

Since OHSS represents a potentially life-threatening condition, prevention still remains the main goal in the management of high risk patients (15). Various solutions to this potential problem have been proposed (Table 1).

The simple use of a reduced dose of hMG for IVF treatment is of limited benefit since a large proportion of the patients show inadequate response (27). The low-dose step-up protocols seem to be more appropriate in anovulatory PCOS patients who need ovulation induction, with satisfactory results (16). Recently, the step-down gonadotropin regimes were proposed as an effective alternative in the management of these patients either with ovulation induction or in-vitro fertilization (17).

The use of GnRH-a in order to alter the ovarian response to stimulation, requires an extremely long period of administration (> 8 weeks), which makes it inconvenient for the patients (12). More recently, the use of GnRH antagonists for ovarian stimulation has been reported to be associated with a lower incidence of OHSS, although in a recent Cochrane review a clear benefit from their use as compared to the long GnRH-a protocols was not shown (18).

HCG is thought to be the main triggering factor for OHSS. Cycle cancellation encloses certain emotional implications for the patients and therefore, valid alternatives were tried. Thus, several manipulations of exogenous ovulatory HCG administration have been proposed for the prevention of an imminent OHSS (15). However, since withholding of ovulatory HCG is accompanied by cycle cancellation, some authors advice to delay HCG with discontinuation of gonadotropins but not of GnRH-agonists, in order to achieve lower E2 levels on the day of HCG administration (20, 12). Large healthy follicles can tolerate with this gonadotrophin deprivation (due to their granulossa cells), but small ones cannot. The result is to reduce the number of the developing follicles, E2 levels and therefore the severity of OHSS, while keeping comparable pregnancy rates. This preventive strategy is now referred to as 'coasting' and is very widely used.

Reduction of the ovulatory HCG dose from 10,000 to 5,000 IU has also been proposed as a preventive measure, but the efficacy of this practice needs to be proved (12).

Several authors have described the use of a short-term GnRH-a administration in order to induce an endogenous LH surge in non-GnRH-a stimulated cycles. This is thought to provide a more physiological hormone milieu, thus avoiding OHSS development (12).

In GnRH-a stimulated cycles, the administration of GnRH-a may be continued after
the ovulatory HCG cancellation, in an attempt to minimize the gonadotropic stimulus on the ovary (2). The value of GnRH-a prolongation in the luteal phase as an additional preventive measure has not been confirmed and is still controversial (19).

Elective embryo-cryopreservation has been proposed as an alternative to cycle cancellation, since the avoidance of pregnancy lessens the incidence and the severity of OHSS in high risk patients (19).

Embryo transfer may be differed in a subsequent unstimulated cycle and the effectiveness of this policy obviously depends on the availability and the efficacy of the cryopreservation program (12). The elective cryopreservation of all embryos from women with high E2 levels reduces the severity but not the incidence of OHSS (28). However, in a recent Cochrane review, it seems that there is insufficient evidence to support the routine use of embryo cryopreservation instead of prophylactic albumin administration or elective fresh embryo-transfer (21).

Alternatively, in cases of mild OHSS it is possible to culture until the blastocyst stage and electively transfer one or two embryos. This practice offers the advantage to follow-up the patients for a more prolonged period, which allows a safer estimation of the severity of OHSS. Moreover, elective transfer of one or two embryos limits the possibility of multiple gestation, which worsens the clinical course of OHSS.

Conversion of ovarian stimulation/intrauterine insemination (IUI) cycles with excessive ovarian response to IVF has been proposed as another option to prevent the occurrence or to reduce the severity of an imminent OHSS (13), by making use of the protective effect of follicular aspiration (12). The repeat aspiration of early corpus luteum cysts at the day of embryo transfer or later in IVF cycles has also been described as an effective preventive measure (22).

The prophylactic administration of albumin is thought to exert a protective effect on OHSS presentation due to its osmotic and binding properties: it draws extracellular fluid into the circulation and may bind and inactivate the vasoactive intermediates responsible for the pathogenesis of OHSS (23). In a recent Cochrane review, it is shown that there is a clear benefit from the administration of intravenous albumin at the time of oocyte retrieval for the prevention of OHSS development in high risk patients (relative risk=0,35) (24).

The suppression of ovarian steroids via the administration of high doses of estrogens plus progesterone during the luteal phase was recently assessed in a prospective randomized study revealing a significant reduce in the incidence and severity of OHSS without compromising the pregnancy rates (25). Nevertheless there is insufficient evidence to support the routine use of these steroids due to lack of adequate data.

Laparoscopic ovarian electrocautery or laser to ovaries, is an option held for women with a history of repeated OHSS. Its rather empirical use makes it a secondary option with no much data available for its effectivity (29).

Lowering the ovarian oestrodiol synthesis, ketokonazole, may lower the cancellation rates in high risk patients for OHSS (30). However due to the limited available data, this new approach needs further evaluation.

The technique of aspirating follicles after an HCG injection and their further maturing in vitro (in vitro maturation of oocytes), has been assessed in PCOS patients giving lowest hyperstimulation incidence. However, continued improvements in laboratory techniques should result in higher implantation and clinical pregnancy rates and therefore reduce the need for numerous oocytes to be retrieved. IVM is a promising reproductive technology. Obviously, more clinical data are needed to support its benefits (31- 34).

**CONCLUSIONS**

Prevention of OHSS starts at the history taking point, clinical and baseline scan examination. Young patients or patients with PCO ovaries need less aggressive regimens avoiding the use of LH preparations. Coasting techniques of HCG and reducing of its ovulatory dose may help. The novel GnRH-antagonist protocols are also promising. Meticulous aspiration of all follicles is necessary
OHSS.

VEGF holds a key role in the development of OHSS. It might be a new treatment strategy, assuming that elimination of post-implantation HCG (phosphatidylinositol-3 kinase) pathway inhibitors, monoclonic antibodies or PI-3K is feasible. Furthermore, the administration of anti-VEGF thus to have practically no OHSS risk. However, 'classical' controlled ovarian hyperstimulation and alternative in high risk patients in order to avoid embryo transfer reduces the severity but not the incidence of OHSS. However, the only preventive measure that has evidence based efficacy is the prophylactic albumin administration.

In Vitro maturation of oocytes could be a viable alternative in high risk patients in order to avoid 'classical' controlled ovarian hyperstimulation and thus to have practically no OHSS risk. However, further development of the technique is necessary. Furthermore, the administration of anti-VEGF monoclonic antibodies or PI-3K (phosphatidylinositol-3 kinase) pathway inhibitors, might be a new treatment strategy, assuming that VEGF holds a key role in the development of OHSS.

### Table 1. Preventive measures for OHSS

**Stimulation Protocol**
- Low dose step-up protocol
- Step-down protocol
- Prolonged administration GnRH-agonist
- GnRH antagonist administration

**Modified administration of preovulatory HCG**
- Reduced HCG dose
- Premature HCG administration
- 'Coasting' approaches
- Cycle cancellation +/- GnRH-agonist continuation

**Triggering ovulation with GnRH-agonists**

**Elimination of post-implantation HCG**
- Withhold embryo transfer +/- cryopreservation of the embryos
- Reduced number of embryos transferred (≤ 2)

**Follicular aspiration**
- Conversion of ovulation cycles to IVF
- Selective oocyte retrieval
- Repeated follicle aspirations

**Luteal phase supplementation**
- Avoidance of luteal phase HCG support
- High dose oestradiol + progesterone administration

**Albumin administration**

**Ovarian Electrosurgery**

**Ketokonazole administration**

**In Vitro Maturation of oocytes**

with or without repetitions before embryo transfer. Cryopreservation of the embryos and deferred embryo transfer reduces the severity but not the incidence of OHSS. However, the only preventative measure that has evidence based efficacy is the prophylactic albumin administration.

In Vitro maturation of oocytes could be a viable alternative in high risk patients in order to avoid 'classical' controlled ovarian hyperstimulation and thus to have practically no OHSS risk. However, further development of the technique is necessary. Furthermore, the administration of anti-VEGF monoclonic antibodies or PI-3K (phosphatidylinositol-3 kinase) pathway inhibitors, might be a new treatment strategy, assuming that VEGF holds a key role in the development of OHSS.

### REFERENCES

Treatment with exogenous gonadotrophic hormones has been used for more than 40 years. It has been more than two decades since they have been the "golden standard" in assisted reproductive techniques. The key issue of using gonadotropins was the improvement of pregnancy rates through retrieval of multiple mature oocytes and increasing the number of replaced embryos (1). However, one of the challenging complications is ovarian hyperstimulation syndrome (OHSS), a dramatic and potentially life-threatening complication. Though the reported incidence of the severe form of OHSS is small (0.5 to 5%), it is an iatrogenic complication of a non-vital treatment (2). Despite a great deal of basic science and clinical research, its pathophysiology is still poorly understood. Since OHSS lacks a specific treatment, prevention has been in focus. Many risk factors have been identified and various methods for preventing OHSS or diminishing its severity have been suggested to avoid withholding hCG and cycle cancellation. Though most of the investigators suggest the use of coating to prevent OHSS, well-designed studies to confirm its preference to other strategies and to standardize application criteria are still lacking (3). Unfortunately, because of inability to consistently identify patients at risk, there is no consensus about its prevention strategies, mostly dealing rather late with the problem when OHSS seems impending, and hence achieve only partial