Iranian Journal of Reproductive Medicine Vol.3. No.2 pp:51-61, 2005

Review article

Prevention is the ideal treatment of OHSS!!!

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is a unique iatrogenic complication of controlled ovarian stimulation (COH)/in vitro fertilization (IVF) in reproductive endocrinology occurring during the luteal phase or early pregnancy. It can have a serious impact on the patient's health.
With the expansion of the assisted reproductive techniques (ART) from 1978, the incidence of OHSS is increasing worldwide.OHSS is characterized by gastrointestinal symptoms, ovarian enlargement, fluid shift to the third space, and hemoconcentration. Severe cases are associated with thromboembolic phenomena, respiratory distress, liver dysfunction and renal failure. OHSS is more common among woman who are young, thin and have PCOS or multiple allergies. Vascular endothelial growth factor (VEGF) and other cytokines are pivotal in the pathogenesis of OHSS.
In the prevention of any disease, it should be emphasized that the possibility of primary prevention depends on two main requirements, first, the etiology of the disease and predisposing factors; and second, it must be feasible to avoid or manipulate such factors as paint of a prevention strategy. This strategy for preventing OHSS and its severity have included prediction of women at risk; the first step in prevention is identification of patients at risk by the recognition of risk factors. As this is not always possible, there are several ways of avoiding developing of the syndrome. The stimulation phase has to be carefully monitored (regular ultrasound and estradiol measurements), and further interventions need to be implemented if signs of hyper-response are present. The aim of this systemic review of the literature is to answer this question: "can we prevent severe OHSS".
Canceling the cycle, modification of method to trigger ovulation administration of macromolecules, coasting approach, timed unilateral or bilateral aspiration of one or two ovaries performed before or after hCG administration, In vitro maturation (IVM), elective cryopreservation of all embryos, and laser or electrocautery of one or both ovaries, have been showed to be associated with a reduced risk of OHSS by some research groups. The effect of combined method should be assessed.

Finally, apart from canceling, none of these approaches was totally efficient, although most of the above-mentioned methods decrease the incidence in patients at high risk of OHSS, but overall "prevention is the ideal treatment of OHSS".

Key words: *Albumin, Coasting, Follicular aspiration, IVF outcome, OHSS, Prevention*

Introduction

The ovarian hyperstimulation syndrome (OHSS) is a rare, iatrogenic, serious and potentially life-threatening complication of ovarian stimulation occurring during the luteal phase or during early pregnancy. The syndrome has been known since 1943, when gonadotrophins were first used to induce ovulation (1). The first fatal cases were described in 1951 by Gotzsche (2). Le Dall, *et al* (1957) described this syndrome in his thesis, and reported acute cases necessitating a laparotomy and unilateral or bilateral oophorectomy or puncture and sutur of ruptured cysts (3). Oliguria and renal failure was the principal complication leading to death at that time.

A World Health Organization report states that the worldwide incidence of sever OHSS is 0.2-1% of all assisted reproduction cycles, which is 1/45,000-1/50,000 mortality per infertile women

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receiving gonadotrophins (4,5). Following in vitro fertilization (IVF), the overall incidence of OHSS is estimated 0.6-14%. Although the prevalence of the sever form of OHSS is very low, it is important to remember that OHSS is usually an iatrogenic complication of treatment.

Today, due to aggressive treatment protocols including the development of IVF and cryopreservation with the goal of obtaining sufficient numbers of oocytes and embryos, an increased risk of assisted developing OHSS is present (6). OHSS is now becoming increasingly more recognized due to the higher number of women undergoing assisted reproductive techniques (ART). The syndrome almost always presents either 3-7 days after hCG administration in susceptible patients (early onset) or during early pregnancy, 12-17 days after hCG administration (late onset). Late OHSS is more likely to be severe than the early form. It is also more difficult to predict from criteria relating to ovarian response (7,8).

The aim of this review is to detail the different strategies used to prevent this serious iatrogenic complication of ART. Recently, there has been a flourish of publications on the issue of OHSS. Very few medical interventation are risk-free and severe OHSS will remain a complication of IVF cycles despite all attempts for its prevention while no strategy for the prevention of OHSS can be guaranteed to work. It should be made clear to the patient that there is a small, but real, risk associated with controlled ovarian hyperstimulation (COH). Finally, since the etiology remains unknown and the pathophysiology is poorly understood, it is not surprising that no strategy has yet been shown to completely prevent the occurrence of severe OHSS.

Epidemiology

The incidence of OHSS is highly variable according to different studies, because various classification are used. In the largest cohort reported, an increase in incidence of sever form of OHSS was observed due to IVF (6). The mild form of OHSS, which have little clinical relevance, constitute about 20-30% of the cases while the moderate form is about 3-6% and 0.1-2% are sever form. Although the incidence of severe forms is low, one should be aware of its recent, progressive increase (9). Identifying the population at risk is the most important step in reducing the incidence of OHSS. It is more common among woman who are young, thin and have PCOS or multiple allergy (10).

A plausible explanation is that the ovaries of younger women are more responsive to gonadotrophins because they possess a higher density of gonadotrophin receptor or a larger number of follicles that are able to respond to gonadotrophins(11).

Most studies agree that young women with lean habitus have a higher tendency to develop OHSS, but no significant difference was observed in BMI in a large Belgian series of 85 OHSS versus 88 controls. BMI does not appear to be a useful marker of increasing risk for OHSS (12).

Classification of OHSS

The first classification of OHSS, which was presented in 1967 (13), combined both laboratory and clinical findings, but later, others recognized and modified the classification into three main clinical categories and six grades according to the severity of symptoms and signs and laboratory findings. The most recent classification with further modification was introduced in 1999 (Rizk and Aboulghar) (14).

A mild degree form of OHSS was omitted from the classification, as mild form can occur in most patients after ovarian stimulation; moreover, the condition had no complications and did not require any special treatment. Sever OHSS was further classified into three grades with distinct definitions: grade A and B were similar to the two subgroups of (others) classification. A new subgroup (Grade C) was then introduced which included OHSS complicated by severe complications such as venous thrombosis and respiratory distress syndrome. Serious complications of OHSS usually occur in sever form of the syndrome, though some (e.g. venous thrombosis) may occur even with moderate OHSS (14).

Etiology

The etiology of OHSS is still unclear. There are several variables closely related to the syndrome, but it should be borne in mind that hCG, either exogenous or endogenous (e.g. pregnancy) is the factor which triggers OHSS. Elimination of hCG will prevent the full-blown picture of OHSS. In fact, when hCG was replaced by progesterone as luteal support in ovulation induction or controlled ovarian hyperstimulatin,

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the incidence of OHSS was reduced, maintaining excellent pregnancy rates (15). If hCG is used for luteal phase support, the risk of OHSS is enhanced.

There are two patterns of the onset of OHSS: early OHSS which generally presents 3 to 7 days after hCG administration and late OHSS, 12 to 17 days after hCG injection. This suggests that there are two mechanisms for the induction of OHSS. Early OHSS is an acute effect of ovulatory hCG and can occur in patients who do not become pregnant. However, late OHSS is induced by endeogenous of hCG from the trophoblast of the implanting pregnancy. This late OHSS is known to resolve rapidly if the pregnancy is aborted, which supports this hypothesis (7,8). We must remember that other stimuli apart from hCG may induce OHSS. As previously studied, endogenous gonadotrophins from gonadotroph adenoma or women with PCOS, as well as elevated TSH levels in women with primary hypothyroidism are potential inducers of OHSS (16).

It is assumed that certain ovarian biosynthetic components, which are produced in excess during induction of ovarian, initiate the cascade of events that result in the syndrome. Recent investigations focused on vasoactive substances, because it is clear that profound alterations in the vascular compartment are the major initial changes that lead to the full appearance and maintenance of OHSS. Thus, hCG may induce the release of a mediator that has potent and direct systemic effects on the vascular system and that may be responsible for the pathophysiology and clinical consequences (17).

Pathophysiology

Although the pathophysiology of OHSS is not well understood, the signs and symptoms of this syndrome can be attributed to local and systemic increase in capillary permeability. These changes, in turn, result in the depletion of intravascular volume at the expense of third space fluid accumulation. OHSS has been directly associated with increasing numbers of stimulated follicles and retrieved oocytes (11), the presence of PCOS (18), and high serum estradiol levels (11,12,19). Despite these associations, however, hyper estrogenemia is not currently thought to be the main cause of OHSS (20). Rather, the increased production of vasoactive substances, such as protein, rennin, angiotensin-converting enzyme, angiotensin I, angiotensin II, and angiotensingen, by the hyper stimulated ovaries has been implicated in this syndrome (21,22). Still, it remain possible that hyperstrogenemia especially in the present of hemoconcentratin, has important effect on the thrombolic risks demonstrated with OHSS. Inflammatory responses are certainly presence in OHSS patients, with possible roles for cytokines, histamine, and prostaglandins in the disease pathogenesis (23). In particular the link between vascular endothelial growth factor (VEGF) and OHSS has been shown to exhibit a dose-related expression in human granulose cells upon stimulatin by hCG. Furthermore, serum VEGF levels correlate with OHSS severity demonstrating a sensitivity and specificity of 100% and 60% respectively (24,25). The central role of an inflammatory response is supported by a number of other facts for instance, mast cells are abundant in ovulatory follicles (26), and histamine blockers has been reported to ameliorate and, in some cases, even prevent OHSS in animal models. Further, it is clinically well recognized that allergy or hypersensitivity act as risk factors for the development of OHSS (11). However, to date, scientific evidence for these factors is still considered preliminary, and further investigation is warranted to clarify their true role in OHSS (20).

A recent epidemiological study showed that women who develop OHSS have an increased prevalence to allergy compared with women with no OHSS (56% vs 21%), respectively indicating that general immunological mechanism may play a role. Mast cells are more abundant in the dominant follicle and could play a role in ovulation. They could hyper-react in the ovary in allergic individuals (11).

Risk factors for OHSS include young age, low body weight, PCOS, higher doses of gonadotrophins, and previous episodes of OHSS (9,18). Risk increases with serum estradiol levels and the number of developing ovarian follicles and when supplemental dose of hCG are administrated after ovulation for luteal-phase support (11,12).

Knowledge and prompt recognition of the risk factors for OHSS are essential for its prevention. Rapidly rising serum estradiol levels, and observation of large number of small and intermediate size ovarian follicles are high risk indicators and signals to proceed with great caution. Cases of recurrent OHSS in spontaneous singleton pregnancy in individuals and families have been described and linked to germline mutations in the FSH receptor resulting in the loss of ligand specificity that permits activation by hCG (27).

Apart from PCOS, patients showing the “necklace sign” in an ovarian ultrasound are at

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increased risk of developing OHSS. Although this finding may be observed in normal ovulatory women with no clinical signs of PCOS, we must be cautious of, stimulating the ovaries of these patients, as the entire cohort of follicles from the necklace may be forced to mature and this multifollicular response can end in OHSS (16).

A new risk factor has been described in women with PCOS. In these patients, the insulinemic pattern may influence the ovarian response to gonadotrophin administration, so that hyperinsulinemic women (diagnosed by an oral glucose tolerance test) are at greater risk of OHSS, than normo-insulinemic patients with PCOS. This may be caused by the effect of insulin on the aromatase activity of granulose cells (28).

Clinical description

In the initial form of OHSS, the increase in size of the ovaries is accompanied by abdominal discomfort. In a more advanced form, the ovaries have become cystic and this will often result in abdominal distention and pain, nausea, vomiting and sometimes diarrhea. These digestive symptoms may be present as soon as 48h after hCG administration, but they become most sever between days 7 to 10 after hCG.

The subsequent clinical signs are likely to result from a circulatory dysfunction corresponding to an increased vascular permeability and marked arterial dilation (29). The first sign of OHSS is the formation of a small amount of ascites which is sometimes only visualized through vaginal ultrasound and difficult to distinguish from the frequent bleeding which occures after oocyte retrieval. In more sever forms, ascites is clinically identifiable, but this is very uncommon before day 7 after hCG administration (14). A series of other complications may occur, some of them ending in complex end organ failure. Ascites is characterized by a high concentration in protein (4.8g/100ml), a low leukocyte count, and the presence of relatively high numbers of red blood cells. The extravascular protein-rich exudates accumulated in the peritoneum, in the pleura and even in the pericardiac space is associated with intravascular volume depletion and homoconcentration, activation of vasoconstrictor and anti-natriuretic factors, severe hypo albuminemia and sometimes vulvar, or generalized edema (30). The cardiovascular effects include arterial hypotension, reduced fluid volume, low central venous pressure, tachycardia, low peripheral resistance, increased vascular stasis, hemoconcentatrion and hyper coagulation. The associated hypovolemia can induce oliguria and electrolyte imbalance. Oliguria exists in about 30% of cases, and renal failure secondary to hypoperfusin or to compressive obstruction occurs in about 1.4% of sever forms of OHSS (31,32). Decreased renal perusing induces a stimulation of renal tubules and resorption of sodium and water that result in clinical manifestations of oliguria and sodium retention. Electrolyte imbalance is then observed, typically hyponatremia and hyperkalemia. Together with ascites, the associated paralytic ileus can impair diaphragmatic movement to such an extent that respiratory problems ensue. If pleural effusion allow develops, lung function may be seriosuly affected and result ultimately in an adult respiratory distress syndrome (ARDS). Pleural effusion can complicate massive ascites or exist as an isolated manifestation of OHSS without peritoneal fluid accumulation, liver dysfunction can also occur. Thromboembolic phenomena are the ultimate complication of OHSS and capable despite appropriate treatment, of killing the patient. So far, a limited number of fatal cases have been reported (33).

Other clinical consequences

Different authors have reported generally compromised obstetric outcome after OHSS. It has been suggested that OHSS may have a detrimental effect on oocyte quality. Lower maturity and quality, resulting in a lower, fertilization rate, have been recently reported. It is generally accepted that OHSS entails very high serum estradiol levels and altered progesterone/estradiol ratio (34). The latter situation has also been reported to be associated with impaired endometrial receptivity (35). Abnormal cytokine levels in patients with sever OHSS may per se affect early pregnancy, further, some gene polymorphism for cytokines (TNF) , has been associated with a higher incidence of pre-eclampsia. Lower pregnancy rate was also found in a group of patients with abnormal liver test and high IL-6 serum concentration (36). A higher incidence of positive markers of thrombophilia were reported (86.6%)among women hospitalized for sever OHSS, and this may be a common risk factor or poor obstetric outcome (miscarriage, pre-eclampsia and placental insufficiency) (37).

PCOS is associated with OHSS, but a higher incidence of miscarriages and pre-eclampsia have been reported in women affected by PCOS. Nevertheless, no all the data concur, as in a recent study to PCOS patients, no difference in the risk of

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miscarriage was observed for women suffering from OHSS and those who did not (38). A higher incidence of miscarriage also result from hypoxia, which is present in sever OHSS, or from dysfunction key organ such as liver and kidney.

The incidence of late OHSS is correlated to the number of gestation sacs, and thus the higher incidence of multiple pregnancies is yet another reason for an increase in poor outcome of pregnancies complicated by OHSS (7,8). Although patients whit OHSS-complicated pregnancies previously reported relatively risk pregnancy induced hypertension (PIH) and gestational diabetes mellitus (GDM) (39), some studies showed the occurrence rates do not differ from a matched control group of normally responding patients who conceived after IVF (40).

In conclusion, the question of whether OHSS it set causes or contributes to any adverse effects on a coexisting pregnancy remains one of the key issues of IVF and is often an important confounding factor. Nevertheless, particular attention should be given to the management of sever OHSS in view of maintaining optimal vital conditions and avoiding hypoxia. Large prospective studies assessing pregnancy outcome must be performed in order to draw definitive conclusions.

Prevention

Clinicians' desire to help their patients achieve a successful pregnancy should be tempered by their responsibility to reduce the risk of potentially life-threatening condition such as sever OHSS and multiple pregnancy. Very few medical interventions are risk-free and sever OHSS will remain a complication of IVF cycles despite all attempts at prevention. How many cases are actually preventable without compromising the patients chances of successful outcome of the intended treatment? A balance between optimum ovarian stimulation and successful treatment outcome in the absence of sever OHSS or multifetal pregnancy is desirable in the practice of ART.

The appropriate stimulation protocol and dose of gonadotrophins need to be chosen for high risk groups. The stimulation phase has to be carefully monitored (regular ultrasound and estradiol measurements), and farther interventions need to be implemented if signs of hyper-response are present.

Overall, the risk of sever OHSS appears to be inherent in the current commonly employed ovarian stimulation protocols that utilize relatively high doses of gonadotrophins, coupled with high risk patients group for example with PCOS. However, it is possible to prevent sever OHSS in high risk patients when ovarian diathermy is performed in the index cycle prior to ovarian stimulation. However, this strategy, yet to be explored further, has the draw back to being surgically invasive with an attendant risk of substantial destruction of ovarian tissue that is required to mute the subsequent response to gonadotrophins (41).

With the introduction in 1987 of GnRH agonist to the COH protocols, clinicians initiated treatment with high doses of gonadotrophins for retrieval of a higher number of mature oocyte (42). Common protocols employed high doses of gonadotrophins combined with GnRH agonist down-regulation a compound that blocks the self-protecting mechanism (spontaneous luteinization) thus preventing further stimulation. The widespread use of routine GnRH agonist protocols have restricted its applicability as a surrogate to hCG to induce final oocyte maturation and ovulation.

However, with the introduction of GnRH antagonist to the protocols it may be prudent in high risk cases to perform COH with GnRH-antagonist in combination with GnRH agonist to trigger ovulation (43,44). Severe methods for preventing OHSS or reduces its side effects has been suggested (45), one of which is canceling the cycle and withholding hCG is the only method which totally avoids the risk of OHSS in ovarian induction cycles or in IVF (46). Furthermore, physicians may also feel more reluctant to propose cancellation to patients as IVF implies a great commitment on the patients' part in terms of procedures, time and money: moreover, the physician are also under pressure to obtain a successful outcome (47). Coasting has been shown to reduce the risk for OHSS in high-risk condition such as rapidly increasing estradil levels or massive follicular recruitment (48).

However, little information exists regarding cycle management and outcome in coasting with immature follicles. In addition, the optimal coast timing and duration has yet to be determined. This technique was first described in 1995 (49). Since then several studies were reported about the types of this technique [early (50,51), late (48), modified (52), prolonged (49)]. There are many advantages to using coasting. First, the cycle is not abandoned. Second, in contrast to cryopreservation, it enables the transfer fresh embryos. Finally, no supplementary procedure or medical therapy is

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involved, in contrast to early follicular aspiration or albumin infusion. It is therefore not surprising that some two-third of physicians who chose to apply a preventive method advocated the use of coasting. Waldenstrom *et al* (1999), amongest other authors have reported sever OHSS still developing in 20% of patients at risk of OHSS in whom the coasting technique was used (53). The reported efficacy of coasting has not been uniformly, consistent probably due to different criteria to apply coasting with estradiol rise from 2500-6000 pg/ml, or leading follicle size ranging from 15-18mm, coasting duration, ranging from 1-11 days (49,53-58). It has been suggested that atresia occurring during prolong coasting (>3 days) maybe associated with impaired outcome of ART. None of these studies were randomized, controlled trials. In the only prospective randomized, controlled trial reported to date that compared prolonged coasting with early unilateral follicular aspiration, the incidence of sever OHSS was similar in both strategies(51,59).The results of Aflatoonian *et al* (2000)confirmed these findings (60).

Recently Mural *et al* (2005) found coasting did not seem to have a detrimental effect on oocyte and embryo quality, because the implantation competence of transferred conceptive after cryopreservation and thawing was similar to that of controls. However, prolonged coasting (>3 days) had a subtle negative impact on the post-thaw survival rate (61).

Various studies have demonstrated a protective value of follicular aspiration or the time of retrieval on OHSS outcome. It may protect agonist OHSS by causing intrafolliculr hemorrhage and granulose cell aspiration (62). By contrast, many authors have claimed that follicular aspiration for IVF dosent for preventing OHSS (63). Tomazevic *et al* (1996) in their observational study described the value of reducing the incidence of OHSS using early timed follicular aspiration (ETFA) of one ovary 10-12h after hCG administration (64). One group performed a prospective randomized study in which unilateral randomized ovarian follicular aspiration was either performed or omitted (controls) at 6-8h before hCG injection. In another prospective randomized study (65), early unilateral follicular aspiration (EUFA) was compared to coasting. Both lines were equally ineffective in the prevention of OHSS (51,60).

Aflatoonian *et al* (2000) reported early bilateral ovarian follicular aspiration (EBFA) of half of follicles 12h before hCG administration in high risk patients. Also they compared EBFA to coasting in randomized prospective study. They concluded that EBFA is as effective as coasting in the prevention of OHSS in high risk patients, but yields higher retrieved oocytes, superior oocytes quality and higher pregnancy rate (66).

In 2003, it was reported that EUFA, before contralateral oocyte retrieval. They concluded EUFA and continuation of stimulation therefore can not be recommended for prevention of OHSS (67). In 2005, a prospective randomized study was performed to evaluate early aspiration of small follicles (EASF), 4 to 7 days after starting gonadotrophins in PCOS patients.These prevented moderate and severe OHSS, and resulted in a higher pregnancy rate (68).

The reduction in estradiol level reported by Gonen *et al* (1991) after follicular aspiration was mostly associated with a similar trend for the precursor molecules (androgen). Low follicular fluid androgen will significantly improve the ongoing pregnancy rate, probably as the result of the improvement in the intra ovarian endocrine milieu, as androgens have a deleterious effect on the quality and maturation of oocyte, embryo quality, and the estrogen- induced endometrial growth and development (69).

The only known difference between the right and left ovary lies in the anatomy of vein. The left ovarian vein drains to the left renal vein and the right sided to the inferior vena cava. In the broad ligament there is a pampiniform plexus on vein (70). Jrvella (2000) showed right-sided ovulation is more frequent than left sided. In addition, this study gives support to the hypothesis that the side of ovulation has an impact on implantation of the embryo. The left ovary appears to act more effectively than right one, as reflected in endometrial thickness in mid-cycle and the pregnancy following freezed/thawed ET (70). By contrast, Mesao *et al* (1998) reported right sided ovulation favor pregnancy more than left side (71). So bilateral follicular aspiration was done (66).

Various studies have demonstrated a protective value of bilateral or unilateral follicular aspiration, before or after hCG injection on OHSS out come. By contrast, many authors has claimed that follicular aspiration for IVF does not prevent OHSS.

It was expected that intraovarian hemorrhage and granulosa cell aspiration would limited the production of ovarian mediator of OHSS (69). The invasive, nature of the method, necessitating two oocyte retrieval (sometimes under anesthesia), is indicative of why this has been attempted less often than coasting.

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In the future, in vitro maturation (IVM) of human oocytes, with and without stimulation, will be avoidable and will several oocytes, there by avoiding hCG administration (72).

Administration of drugs

Human albumin infusion before or after oocyte retrieval was proposed a few years ago as a safe, effective, and economical treatment for prevention of sever OHSS in high risk patients. Excellent reviews on this subject are available, and they do not suggest a role of prophylactic I.V. albumin in sever OHSS, according to the published evidence (73).

Aboulghar *et al* (2005) showed a clear benefit from administration of intravenous albumin at the time of oocyte retrieval in prevention of severe OHSS (74). The recent evidence are potentially more worrying that human albumin may increase mortality in critically ill patients. The committee on safe of medicines expect working part has excluded that special care should be taken when administering albumin in pathological states which effect capillary integrity (75). Other plasma expanders such as hydroxyethyl starch solution (HES) have been assayed in primary prevention of sever OHSS. Some authors reported a prospective, randomized trial in which 6% HES significantly reduced the incidence of moderate to severe OHSS in patients undergoing ART (76). The administration of some drugs were reported for preventing sever OHSS, such as Docarpaimin (dopamine prodrug) by causing renal and mesenteric vasodilatation as well as diuretic effect (77).Also in 2005 adiministration of Letrazol for the replacement of clomiphen citrate in PCOS cases was reported (78). Clomiphen citrate is only rarely associated with severe OHSS. Three possible contenders for the replacement of clomiphen citrate as first-line treatment are scrutinized: metformin, new aromatase inhibitors such as Letrazole, and low dose FSH. Recently Navortis has warned doctors not to use letrazole to help women become pregnant after report of adverse events (79).

Triggering of ovulation

There is enough evidence in the literature to identify hCG as the main triggering cause of OHSS, probably through other less-known mediators, where an endogenas LH surge rarely Cause OHSS. hCG is characterized by a longer half-life than endogenous LH (>24h versus 60 min for LH) , a higher receptor affinity, and a longer duration of intracellular effect (80). Normal doses of hCG are 10.000 IU, but doses ranging from 2,000 to 25,000 IU have been used. The pregnancy rate seems not to vary for doses >5000 IU (81).

One group reported fewer cases of OHSS when using 1000-5000 IU, but this study was not controlled; hence it has been suggested that a dose of 5000, rather than 10,0000 IU be used in the presence of risk factor for OHSS (82).

In a randomized study using the long GnRH protocol, a low dose of recombinant hCG (rhCG) (250µg) was found to be as effective as 10000 IU urinary hCG in triggering ovulation, moreover, the pregnancy rate, implantation rate and OHSS rate were similar (83).

Neither moderate nor severe OHSS was reported in patients who received a single dose of rhLH up to 30000 IU. These results showed that a single dose of rhLH was effective in inducing final follicular maturation and early luteinization in IVF patients, and was comparable with 5000 IU urinary hCG. A single dose of rhLH resulted in a highly significant reduction in OHSS compared with hCG (84).

The new treatment option for patients undergoing ovarian stimulation was used to eliminate the risk of developing OHSS in high responders. A preliminary report describes the use of 0.2 mg triptorelin (decapeptyl) to trigger ovulation in eight patients who underwent controlled ovarian hyperstimulation with recombinant FSH and concomitant treatment with the GnRH antagonist ganirelix for the prevention of premature LH surge (85). GnRH-a induce surges of endogenous LH and FSH, with similar luteal phase length and progesterone levels as hCG cycles. GnRH-a may be an acceptable substitute in cycles of ovulation induction to trigger ovulation in women at risk, although they are not applicable to COH protocols with GnRH-a suppression. The relatively short half-life (3 to 5 hours) eliminates the risk of OHSS in non-conception cycles. Ovulation rates close to 75% and pregnancy rates around 17% have been reported, with a low rates of multiple pregnancy. No women developed OHSS in this short series (86).

Cryopreservation of all embryos for future transfer

As OHSS syndrome is more common in conception cycles due to the endogenous hCG from the trophoblast of the implanting pregnancy, elective cryopreservation of all embryos has been

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postulated. It is not expected that elective cryopreservation would have any influence on early OHSS, which is an acute effect of exogenous hCG from the trophoblasts In all but one report the rate of pregnancy after frozen-thawed embryo replacement was as high as when using fresh embryo. There is insufficient evidence to support routine cryopreservation, to determine the relative merits of intravenous albumin versus cryopreservation (45).

Single blastocyst transfer is proposed as a method to decrease multiple pregnancy and the authors conclude that the risk of late OHSS can be eliminated. It is correct that with postponement of transfer, the patient can be evaluated and transfer considered or postponed. Some authors found single embryo transfer (SET) with a subsequent decline in twin pregnancies would result in a lower incidence of OHSS. The population at risk remains the same. The overall pregnancy rate remained stable at 31.3% while the multiple pregnancy rate decline from 33% to 11.7% (87).

Some authors recently found that, unfortunately, singleton pregnancies are affected by OHSS as frequently as twin pregnancies. This is probably because the patients at risk for OHSS are the same but receive only one embryo to transfer. The risk for OHSS in patients at risk rather than to the threshold value of hCG in patients at risk rather than to the number of embryo transferred (45).

Luteal phase supports

Ovarian stimulation results in multifollicular development and higher steroid serum concentrations than natural cycles. Defects in the luteal phase, which have been described in virtually all stimulation protocols, may be attributed either to an altered hormonal environment or to a direct drug effect (16).

Luteal phase deficiency is a common feature of cycles resulting from stimulation of follicular development. It has been reported in cycles stimulated with HMG/FSH alone, in cycles down-regulated with a GnRH agonist and stimulated with HMG/FSH (88), as well as in cycle using a GnRH antagonist in combination with HMG/FSH (89). Luteal phase supplementation or support is therefore common practice in infertility treatment to significantly improve embryo implantation rates, clinical pregnancy rates and delivery rates (88). Two therapeutic agents are routinely used to supplement the luteal phase; natural progesterone and hCG. Vaginal administration of progesterone is probably as effective as I.M. progesterone in multiple daily application. Whether the efficacy of a single daily administration has been questioned. HCG is a promoter of OHSS, and luteal supplementation using a single injection or repeated doses of this hormone exacerbates OHSS (90). In one retrospective study, 12% and 0% severe OHSS was observed respectively when the luteal phase was supported by hCG or progesterone (15). Others, in a randomized prospective study observed respectively 28% and 0% of moderate and severe OHSS in the same conditions (91). It is also known that patients with severe OHSS, who did not become pregnant generally, received exogenous hCG for luteal support.

Finally, a recent review concerning luteal phase support confirmed that, excepting oral progesterone , results are similar in terms of implantation and clinical pregnancy rates, whether HCG, vaginal or intramuscular progesterone is used. However progesterone was deemed to be the best choice as it is associated with a lower incidence of OHSS (92).

In 2003 a prospective randomized study was carried out to evaluate the efficiency of high dose progesterone and estradiol administration during the luteal phase to prevent OHSS. These results indicate a promising tool to reduce the incidence and severity of OHSS in a high-risk population without compromising the pregnancy rate (93).

Also, in 2005, native GnRH has been used to support the luteal phase support.In one study this study suggests that testing the use of a GnRH agonist as luteal support in ART appears feasible (94).

Conclusion

OHSS is an iatrogenic and potentially dramatic clinical condition. Despite the well-established predictive value of such markers, some OHSS cases cannot be anticipated before the initiation of ovarian stimulation. In the late 90's COH protocols tended to be more aggressive (42), relying on numerous preventation tactics which were never proven, such as albumin infusion, coasting, early ascites aspiration, follicular aspiration, GnRH agonist administration as surrogate to hCG, and so on. Common protocols employed high doses of gonadotrophins combined with GnRH agonist down-regulation. There is no doubt that incidence of OHSS is related to type of stimulatory regimen use, modification of ovulation triggering and luteal phase support. The first step in prevention is identification of patients at risk by the recognition of risk factors.

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With the introduction of GnRH antagonist to protocols it may be prudent in high risk cases to perform COH with a GnRH antagonist in combination with GnRH agonist to trigger ovulation (43,44).

The reported efficacy of coasting has not been uniformly consistent, probably due to different criteria for applying coasting. It has been suggested that atresia, occurring during prolonged coasting, may be associated with impaired outcome of ART. There is insufficient evidence to determine whether coasting is an effective strategy for prevention OHSS or not (56-61).

Follicular aspiration lead to significant reduction in serum E2 and other hormones. Therefore different investigation has managed to reduce but not eliminate the risk of sever OHSS by bilateral or unilateral aspiration of follicles, before or after hCG administration. Various studies have demonstrated a protective value of follicular aspiration on OHSS outcome. By contrast, many authors have claimed that follicular aspiration does not prevent OHSS (63-69). Since the etiology remains unknown and the pathophysiology is poorly understood, it is not surprising that no strategy has yet been shown to completely prevent the occurrence of severe OHSS.

Finally apart from canceling, none of these approaches was totally efficient, although most of them decrease the incidence of OHSS in high risk patients. There is a clear need for large prospective randomized studies to be conducted that would compare different modalities in women at high risk of OHSS, thus providing evidence-based practice. But at the moment; prevention is the ideal treatment of OHSS.

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