Ovarian hyperstimulation syndrome: pathophysiology and prevention

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Abstract

Purpose To review and discuss the pathophysiology and prevention strategies for ovarian hyperstimulation syndrome (OHSS), which is a condition that may occur in up to 20% of the high risk women submitted to assisted reproductive technology cycles.

Methods The English language literature on these topics were reviewed through PubMed and discussed with emphasis on recent data.

Results The role of estradiol, luteinizing hormone, human chorionic gonadotropin (hCG), inflammatory mediators, the renin-angiotensin system and vascular endothelial growth factor is discussed in the pathophysiology of OHSS. In addition we consider the prevention strategies, including coasting, administration of albumin, renin-angiotensin system blockage, dopamine agonist administration, non-steroidal anti-inflammatory administration, GnRH antagonist protocols, reducing hCG dosage, replacement of hCG and in vitro maturation of oocytes (IVM).

Conclusions Among the many prevention strategies that have been discussed, the current evidence points to the replacement

of hCG by GnRH agonists in antagonist cycles and the performance of IVM procedures as the safest approaches.

Keywords Ovarian hyperstimulation syndrome · Ovulation induction · Assisted reproductive techniques

Introduction

Ovulation induction therapy is one of the most important processes for assisted reproduction cycles. A certain degree of ovarian hyperstimulation is desirable during these procedures, however, an exaggerated response poses a risk of the potentially life-threatening ovarian hyperstimulation syndrome (OHSS) and must be avoided. 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 [1, 2]. Among high risk women the incidence approaches 20% [3]. This syndrome occurs almost exclusively during assisted reproductive technology (ART) cycles, although OHSS might also can occur during ovarian stimulation using clomiphene citrate [1] and even in a spontaneous pregnancy [4].

Conditions associated with a higher risk of OHSS include the following: young age, low body mass index, higher doses of exogenous gonadotropins, high absolute or rate of increase of serum E2 levels, and previous episodes of OHSS [5]. Physicians who treat infertile women should understand the pathophysiology of OHSS to avoid this iatrogenic condition.

OHSS physiopathology

Some degree of ovarian hyperstimulation occurs in all women who respond to ovulation induction, but this should

Capsule Many strategies have been suggested to prevent OHSS. Based on current evidence, replacement of hCG by GnRH agonists in antagonist cycles and IVM are the safest approaches.

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be distinguished from OHSS [6]. Increased capillary permeability and ovary enlargement are the principal characteristics of OHSS. Fluid escapes from vessels into the third space, resulting in hypovolemia [7, 8]. While mild OHSS lacks clinical relevance, severe OHSS is characterized by massive ovarian enlargement, pleural effusion, ascites, oliguria, hemoconcentration and thromboembolic phenomena. Some possible causal factors are listed below and summarized in Table 1.

Estradiol

Initially the role of estradiol in the pathophysiology of OHSS roused great interest, as a high level of this sex hormone has been strongly associated with this syndrome [9]. This association led researchers to believe that the elevation in estradiol concentration caused this syndrome. However, it was demonstrated that estradiol is not necessary for OHSS development; a women with 17,20-desmolase activity deficiency had OHSS during in vitro fertilization despite low levels of estradiol [10]. Additionally, high levels of estradiol alone did not result in OHSS, which only occurs if hCG is also elevated [6]. Nowadays the association between increased levels of serum estradiol and OHSS is considered a mere marker of granulosa cell activity [11]. However, elevated estradiol concentration is still considered one of the best predictors of OHSS occurrence, as at risk women demonstrate high absolute (>2,500 pg/mL) or rapidly rising serum estradiol levels [5].

LH and hCG

The hormone hCG is used during ART cycles to stimulate LH receptors to initiate the final stages of follicle and egg

maturation. The biological activity of hCG is approximately six to seven times higher than LH as a consequence of its longer half-life and affinity for the receptor [11]. Despite the fact that hCG is considered to be fundamental in triggering OHSS, this hormone alone is unlikely to cause OHSS. In an evaluation of 27 gestations with hCG concentrations higher than 150,000 IU/L (with a max of 344,350 IU/L), no woman developed spontaneous OHSS [4]. However, in the same article the authors did report a case of OHSS in a spontaneous pregnancy; a 36-year-old women in the 10th week of gestation. This was the fifth case reported in the literature.

Inflammatory mediators

Some immune system products are implied in the pathophysiology of OHSS. A number of cytokines are associated with the inflammatory process that takes place during the late follicular maturation, ovulation, corpus luteum function, and embryo implantation [11]. Some interleukins may be found in elevated concentration in patients with OHSS, and increased expression of interleukin 6, for example, is associated with increased vascular permeability, hemoconcentration, elevated plasma estradiol concentration, and inhibition of hepatic albumin production [12].

Renin-angiotensin system

A direct correlation between plasma renin activity and the severity of OHSS was described more than two decades ago [13]. Ovaries are able to synthesize pro-renin [14] and renin [15]. Additionally, the follicular and ascitic fluid concentration of angiotensin II are higher than the plasma concentration in women with OHSS [15], and elevation of

Table 1 Described causal factors for ovarian hyperstimulation syndrome (OHSS)

Estradiol	Estradiol level is a reliable predictor of OHSS during ART [5] OHSS can occur despite low estradiol levels [10] High estradiol concentrations are not sufficient to induce OHSS [6] Currently considered a mere marker of granulosa activity [11]
hCG	Fundamental for triggering OHSS hCG alone is not sufficient to induce OHSS [4]
Interleukins	Some interleukins are associated with OHSS, and elevated concentrations are associated with increased vascular permeability, hemoconcentration, elevated plasma estradiol concentration, and inhibition of hepatic albumin production [12]
Renin-angiotensin system	There is a direct correlation between plasma renin activity and the severity of OHSS [13] All hypovolemic conditions are associated with a secondary reactive hyperaldosteronism via renin-angiotensin cascade activation [17] Renin-angiotensin system activation is probably the effect and not the cause of OHSS
VEGF	VEGF expression is associated with OHSS increased vascular permeability [18] VEGF levels are elevated during ovarian stimulation with exogenous FSH, which is enhanced after hCG administration [19, 20]

plasma angiotensin-converting enzyme was reported in a case of severe OHSS [16]. However, renin-angiotensin system activation is probably an effect of and not the cause of OHSS. All hypovolemic conditions are associated with a secondary reactive hyperaldosteronism by renin-angiotensin cascade activation [17].

Vascular endothelial growth factor (VEGF)

Since the description of the association between OHSS, increased vascular permeability and VEGF expression [18], several studies have aimed to clarify this relationship. Studies initiated in rodents [19] and confirmed in humans [20] have shown that vascular permeability, VEGF and VEGF receptor (VEGFR) levels are already elevated during the gonadotropin stimulation phase, preceding hCG injection.

However, these parameters are further stimulated by hCG administration. Preceding stimulation, VEGFR may be found only in the corpus luteum vessels, but after hCG stimulation these receptors may be found throughout the corpus luteum [20]; additionally, peak expression for both VEGF and VEGFR occurs approximately 48 h after hCG injection [19].

VEGF causes an increase in vascular permeability by rearranging endothelial junction proteins, including cadherin and claudin 5. When evaluating human endothelial cells from umbilical veins (used as an *in vitro* model of OHSS), hCG and VEGF caused changes in the actin fibers that are indicative of increased capillary permeability, and cadherin concentration was elevated when hCG and VEGF were added, but not with the addition of estradiol [21]. A more recent study demonstrated that hCG leads to an augmentation in VEGF concentrations and vascular permeability when studying *in vitro* models (luteinized granulosa and human umbilical vein endothelial cells), which was related to reduced claudin 5 expression in endothelial cells [22].

Prevention strategies

The most important aspects of OHSS prevention are sound clinical judgment with ovulation induction and acknowledgment of the risk factors [5]. In the face of a high risk for OHSS situation, many strategies have been reported to decrease the risk of OHSS (Table 2).

Coasting

“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 [23].

During this period gonadotropin administration may be reduced or withheld. In a retrospective study [24], withholding gonadotropin for at least 3 days in high-risk women was associated with a 63% reduction in the plasma estradiol concentration (from 18,043 to 6,656 pmol/L), while a reduction of only 29% (from 14,205 to 10,132 pmol/L) was observed among high-risk women that continued to receive gonadotropin. Regarding the duration of coasting, withholding gonadotropin administration for, at most, three days may decrease the risk of OHSS without modifying the pregnancy rate. However, withholding for four or more days is associated with a lower implantation rate, probably because of the effect on endometrial receptivity [23].

The application of coasting is usually indicated by the plasma estradiol level on the day of the gonadotropin administration. However, there is no consensus regarding a minimal value to indicate that gonadotropin administration should be withheld. In most published articles, the estradiol cutoff value is somewhere between 2,500 and 4,000 pg/ml [3, 25, 26].

The reason for OHSS prevention by coasting remains uncertain. Increased rate of apoptosis in all ovarian follicles, particularly those under 14 mm in size, is cited as a possible mechanism for the effects of coasting. As those follicles are primarily responsible for the high serum concentration of estradiol and vasoactive compounds, there is a consequent reduction in both serum estradiol concentration and in follicular secretion and gene expression of VEGF [27]. Although coasting is one of the most common strategies for preventing OHSS and is considered to be of great benefit because a significant decrease in estradiol levels is clear, there are a lack of randomized controlled trials (RCT) in which coasting is compared to not coasting. The evidence is still insufficient to determine whether coasting is an effective strategy for preventing OHSS [28], and the incidence OHSS can be as high as 9.4% even with coasting [29].

Albumin administration

Albumin is a low molecular weight plasma compound with a major impact on oncotic pressure. Human albumin has been used on the day of hCG administration in high-risk women to prevent OHSS. However, its efficacy is still a matter of debate. A review article published in 2002 [30] included five RCTs and evaluated the use of albumin in 193 women and 185 controls. The odds ratio for OHSS in the group treated with albumin was 0.28 (95%IC 0.11–0.73). According to this study, eighteen high-risk women must be treated to prevent one case of OHSS.

However, subsequent clinical trials have not shown any benefit in its use [31, 32]. In one of these studies, a RCT that included 998 high-risk women [32], the administration

Table 2 Prevention strategies for ovarian hyperstimulation syndrome (OHSS)

Coasting	Postpone hCG administration until estradiol levels are secure During this period gonadotropin may be reduced or withheld Coasting clearly decreases estradiol levels Coasting for up to three days does not negatively interfere with pregnancy rates [23] Evidence is still insufficient to determine whether or not coasting is an effective strategy for preventing OHSS [28] and OHSS can occur in up to 9.4% of patients even with coasting [29]
Albumin	Human albumin has been used on the day of hCG administration in high-risk women, as a method of OHSS prevention The best currently available evidence shows that albumin administration does not decrease the incidence of OHSS [32]
Renin-angiotensin system blockage	Two cases series have reported the use of a dual blockage combining the use of an angiotensin receptor blocker and an angiotensin converting enzyme inhibitor Moderate/severe OHSS occurred in 14.4% of cases [33, 34] Drugs have potential harmful effects to the fetuses and may worsen an OHSS associated renal failure [17]
Dopamine agonists	Cabergoline inhibits partially the VEGF receptor 2 phosphorylation levels and associated vascular permeability without affecting luteal angiogenesis [35] Reduction on the ‘early’ (within the first 9 days after hCG) onset of OHSS [36] Even using cabergoline, the OHSS incidence may be as high as 10.8% [36]
Non-steroidal anti-inflammatory	A large RCT demonstrated that low dose aspirin was associated with reduction in the OHSS incidence (0.25% vs. 8.4%) in a high-risk group with similar pregnancy rates [37] Meloxicam was capable of reducing the OHSS associated ovarian weight and expression of VEGF in an animal model [38]
GnRH antagonist protocol	This regimen is associated with a significant reduction in OHSS (Odds Ratio=0.60) as well as with fewer interventions to prevent OHSS (OR=0.43) However a slight reduction in pregnancy rates was also observed (OR=0.83) [39]
Replacement of hCG	A single dose of recombinant LH was safer than hCG and was effective in inducing follicular maturation The dosage of 15,000–30,000 IU is still too expensive [42] Using a GnRH agonist to induce final oocyte maturation, no cases of moderate/severe OHSS were observed in 1,152 cycles of oocyte donation against 14 cases in 1,137 cases who received hCG [43, 44]. This requires the use of GnRH antagonist protocol.
In vitro maturation of oocytes	Benefits include the fact that this is a simple protocol with decreased or no hormonal stimulation before oocyte retrieval leading to a lower cost for the treatment cycle. The risk of OHSS is entirely avoided [48] IVM is not a widely used fertility treatment, since there is a lower chance of a live birth per treatment compared with conventional in vitro fertilization and human oocytes collected from the unstimulated ovary have higher rates of meiotic spindle and chromosome abnormalities [47] Recent publications have shown very good pregnancy per embryo rates of about 40% with hCG priming [49, 50]

of 40 g of human albumin immediately after the oocyte retrieval was compared with no treatment. After a seven-day follow-up no significant difference could be detected in the rate of hemoconcentration, liver or renal dysfunction, or in the incidence of moderate or severe OHSS between the two groups (the incidences of moderate-severe and severe-only OHSS were identical between the groups). The authors concluded that the infusion of albumin on the day of oocyte retrieval is not a useful means to prevent OHSS.

Renin-angiotensin system blockade

Two series of cases [33, 34] have reported the use of a dual blockage combining the use of an angiotensin receptor blocker and an angiotensin-converting enzyme inhibitor. Considering both studies, fourteen high-risk women (estra-

diol >8,000 pg/ml) were studied, and two cases of moderate/severe OHSS occurred (14.4%). In both studies, the embryos were cryopreserved and transferred in subsequent cycles. However, the activation of renin-angiotensin system is probably the effect and not the cause of OHSS, and one should be cautious when considering this strategy, since there are harmful effects to the fetuses and the possibility of worsening OHSS associated renal failure [17].

Dopamine agonist administration

After the demonstration of the partial inhibition of ovarian VEGF receptor 2 (VEGFR-2) phosphorylation levels by the dopamine agonist cabergoline in an animal model [35] and its consequent reversion of VEGFR-2 vascular permeability

without affecting luteal angiogenesis, cabergoline was then studied in the clinical setting. A randomized, controlled clinical trial [36] was performed using cabergoline 0.5 mg daily for 3 weeks beginning on the day after oocyte retrieval compared with no treatment. Both groups presented similar pregnancy, implantation and miscarriages rates. ‘Early’ OHSS (within the first 9 days after hCG administration) was significantly lower in the group treated with cabergoline (0.0% vs. 14.5%). No difference was observed in either the incidence of ‘late’ OHSS (after 10 days of hCG administration), which was 10.8% in the treated group and 3.6% in the control group, nor in overall OHSS cases—10.8% in the cabergoline group and 18.1% in the control group.

Non-steroidal anti-inflammatory administration

Low-dose aspirin therapy (100 mg daily, beginning on the first day of ovarian stimulation) was shown to be effective in preventing OHSS among high risk women in a recent, large RCT [37]. This study evaluated 2,425 cycles in which gonadotropin-releasing hormone agonist was used. Among 1,192 women at a high risk for developing OHSS, 780 randomly received aspirin, and the incidence of OHSS was 0.25% compared with 8.4% among the 412 women who did not receive aspirin. The pregnancy rates were similar. Meloxicam is another anti-inflammatory drug that was studied in an animal model [38], where it was demonstrated to be capable of reducing the OHSS associated ovarian weight and expression of VEGF.

GnRH antagonist protocol

GnRH antagonists cause immediate suppression of gonadotropin secretion. They are used after exogenous stimulation has begun and consequently shorten the total duration of treatment. A recent meta-analysis [39] reported a discreet worsening in pregnancy rates when GnRH antagonist regimens were compared to the standard long protocol (OR=0.83; 95% CI=0.72–0.95), and a significant reduction in severe OHSS was also reported (OR=0.60, 95% CI 0.40–0.88) as well as fewer interventions to prevent OHSS (OR=0.43, 95% CI 0.20–0.92). Additionally, when using GnRH antagonist protocols one may induce oocyte maturation with GnRH agonists, since this drug is not used to block pituitary secretion during ovarian stimulation. This issue will be discussed later.

Reducing hCG dosage

Concerning ovulation induction, the historical dosage of hCG is 10,000 IU. A reduction in this dosage has been proposed, ranging from 5,000 to 2,500 IU. In a retrospec-

tive study of 250 cycles, the habitual hCG dose of 5,000 IU was compared to a reduced dose of 3,300 IU, given to women whose serum estradiol concentrations were between 4,000 and 5,500 pg/mL [40]. The proportion of mature oocytes, fertilization rates and pregnancy were not different between the two groups; showing that reducing hCG dosage does not worsen IVF results. More recently, a pilot study evaluated the safety and efficacy of hCG dosages of 2,500 IU in 21 high risk women [41]. No moderate or severe OHSS was observed, and a high pregnancy rate was reported (61.9%), allowing the authors to conclude that this strategy does not worsen IVF results and may reduce OHSS incidence.

Eliminate hCG

OHSS complications could be theoretically eliminated if hCG was not used, since no moderate or severe form of OHSS was observed without the administration of this hormone. Recombinant LH could be a safer surrogate for hCG, but using recombinant LH is not economically feasible. Nevertheless, the equivalent dosage to 5,000 IU of hCG would be between 15,000 and 30,000 IU of recombinant LH [42].

GnRH agonist could be used to induce oocyte maturation instead of hCG during a GnRH antagonist protocol. Replacing hCG with GnRH agonists was shown to be financially acceptable, with good pregnancy rates and a dramatic decrease in severe and moderate OHSS [43–45].

Two studies evaluating 2,289 stimulation cycles using GnRH antagonist regimens in egg donors—a retrospective cohort study of 2,077 cycles [43] and an RCT of 212 cycles [44]—compared the ability of hCG and GnRH agonists to induce final oocyte maturation. A significant reduction in the moderate and severe form of OHSS was reported; when GnRH agonists were used, no cases of OHSS were observed versus fourteen cases in the hCG group (thirteen in the retrospective cohort and one in the RCT). The only other significant difference was a minor increase in the fertilization rate in the GnRH agonist group in the retrospective cohort (65% vs. 69%; hCG vs. GnRH agonist, respectively) which was also observed in the RCT (67.8% vs. 71.1%, respectively), but the differences were not statistically significant.

No moderate or severe OHSS was observed when women at a high risk for OHSS used GnRH instead of hCG [45, 46]. In one RCT, 66 women at a high risk for OHSS with polycystic ovarian syndrome (PCOS) or a previous high response undergoing IVF were evaluated [45]. The women were randomized to either hCG to induce final oocyte maturation in a standard long GnRH antagonist protocol or to GnRH agonist in a GnRH antagonist regimen. Only women who received hCG

developed any form of OHSS (31%, 10 of 32). No significant differences were observed in the following fertility outcomes: implantation (36.0% vs. 31.0%, GnRH agonist vs. hCG, respectively), clinical pregnancy (56.7% vs. 51.7%, respectively), or ongoing pregnancy rates (53.3% vs. 48.3%, respectively). The other study was a retrospective observational study that evaluated 42 women with PCOS who had a previously experienced a cycle that had had to be cancelled because of an elevated risk of OHSS [46]. Women were submitted to the antagonist protocol and GnRH agonist to induce final oocyte maturation: all of them completed oocyte retrieval, and no women developed OHSS. The embryos were cryopreserved and transferred in a later cycle.

In vitro maturation of oocytes (IVM)

The safest way to prevent OHSS would be by not stimulating the ovaries. During an IVM cycle, immature oocytes are retrieved from barely stimulated or completely unstimulated ovaries. The oocytes are matured in defined culture media for 24–48 h and then fertilized by in vitro fertilization or intracytoplasmic sperm injection. The embryo transfer is performed as usual; normally two embryos are transferred in two or three days after fertilization. The lack of ovarian stimulation during IVM cycles brings many benefits, including the following: reduction in medication cost, no risk for OHSS, and a reduction in the total number of patient visits for clinical and laboratory evaluations [47].

Clinical trials evaluating IVM performed in women with PCOS demonstrated good pregnancy ratio per embryo transferred (20–54%) and good implantation rates (5.5–34.5%) [48]. When evaluating IVM performed in ovulatory women, the results were a little worse, with pregnancy per embryo transfer rates between 15 and 33.3% and implantation rates between 8.8 and 22.6%. The literature reported the birth of approximately 400 children using IVM and the postnatal follow-up studies of the children have been reassuring [48]. The improvement in the pregnancy rate reported in recent publications resulted from better laboratory techniques and clinical management. The use of hCG before oocyte retrieval resulted in higher maturation rates, and better endometrial preparation resulted in higher implantation rates, which raised the clinical pregnancy per embryo transfer rate to about 40% [49, 50]. Although good results have been reported by some clinics, IVM has not yet become a mainstream fertility treatment. The most important reasons are: 1- technical difficulties for retrieving immature oocytes from unstimulated ovaries and to cultivate them; 2 - lower chance of a live birth per treatment compared with conventional in vitro fertilization; 3- the report of higher

rates of meiotic spindle and chromosome abnormalities from immature human oocytes [47].

Conclusions

The occurrence of OHSS may be considered the most serious complication related to assisted reproduction techniques. Ovarian stimulation procedures for oocyte retrieval are expensive and represent a heavy emotional burden for all people involved. Minimizing the risk of OHSS is a key issue, especially for those women considered to be high-risk—the chance of developing the syndrome may be as high as 20%—and also for those who undergo these procedures with the aim of oocyte donation. We believe that to eliminate the occurrence of OHSS while maintaining acceptable costs; we should put effort into the study and the elaboration of feasible protocols with the administration of GnRH antagonists and agonists and the realization of IVM procedures in women at high risk. However, large prospective controlled trials are needed to attest to the efficacy of these protocols and to assure that OHSS may be completely avoided by these means.

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