Prevention and Management of OHSS

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most frequent and life-threatening complications of controlled ovarian hyperstimulation (COH). OHSS is characterized by increased capillary permeability and resulting fluid shifts into the abdominal cavity that is in large part mediated by the overexpression of vascular endothelial factor (VEGF) in the overstimulated ovary. Severe cases can result in electrolyte derangement, haemoconcentration, and renal and hepatic dysfunction, requiring hospitalization and close inpatient monitoring. The incidence of OHSS has been reported to be as high as 20–33% for mild cases, 3–6% for moderate cases, and 0.1–2% for severe cases [1]. Several strategies have been proposed to prevent OHSS. These include individualizing ovarian stimulation protocols, coasting, cycle cancellation, and the use of GnRH agonist and/or low-dose hCG triggers.

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Identifying Patients at Risk

Women at risk of developing OHSS can be targeted prior to ovarian stimulation to employ strategies to decrease the likelihood of developing the syndrome. Several factors, including history of prior OHSS, patient demographics (i.e. young age and low body weight), and polycystic ovary syndrome (PCOS), can predict the risk of OHSS. One meta-analysis demonstrated a 6.8-fold increased risk of OHSS in PCOS patients compared to women with other infertility diagnoses [2].

Serum markers may be used to predict the risk of OHSS. These include day 3 FSH, inhibin B, and anti-Mullerian hormone (AMH). Lee et al. [3] reported AMH and serum E2 as the most reliable predictors of OHSS in a study in patients undergoing agonist IVF protocols. They showed basal serum AMH level >3.36 ng/mL predicted OHSS with a sensitivity of 90.5% and specificity of 81.3%.

Secondary risk factors related to ovarian response include ultrasound and serum measures during ovarian stimulation. These include high number of follicles (greater than 20 follicles measuring over 10 mm), high or rapidly rising serum E2 (>3000 pg/mL), and number of oocytes retrieved [4]. Ho et al. [5] reported that high mid-follicular levels of E2 (>800 pg/mL on day 6 of gonadotropin stimulation) were associated with an increased risk of OHSS. Identification of risk factors is essential for primary prevention of OHSS. Patients at risk are the

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candidates for preventive measures which can decrease the risk of OHSS, as outlined below.

Individualizing Gonadotropin Dosing

With the introduction of gonadotropin-releasing hormone agonists (GnRHa) to IVF protocols in the late 1980s, higher doses of gonadotropins were used to yield more mature oocytes and lower cancellation rates [6]. However, higher doses of gonadotropins were associated with an increased risk of OHSS. In response to this, protocols were individualized with the goal to use minimal gonadotropin dosing to achieve the best oocyte quantity and quality while avoiding risks of OHSS. The CONSORT trial utilized an algorithm designed to individualize dosing of recombinant human FSH in increments of 37.5 IU according to basal FSH, body mass index, age, and antral follicle count [7, 8]. The results of this study demonstrated similar clinical pregnancy rates compared to that of a standard approach.

The use of GnRH antagonists to prevent the endogenous luteinizing surge has also been shown to reduce the risk of OHSS [9]. This allows for shorter duration of stimulation without compromising oocyte yield or overall pregnancy rates [10, 11]. GnRH antagonists are usually introduced into the IVF cycle once the leading follicle is 12–14 mm while E2 levels exceed 300 pg/mL. Using a GnRH antagonist protocol also provides the option to use a GnRH agonist trigger to induce final oocyte maturation, thus avoiding the use of hCG. Two meta-analysis reported a lower incidence of OHSS with the use of a GnRH antagonist, including women with PCOS [12, 13]. However, a Cochrane review in 2007 corroborating the above findings revealed a lower pregnancy rate when compared to GnRH agonist treatment [14]. Thus, GnRH antagonist protocols are effective in reducing the risk of OHSS; however, it may compromise overall pregnancy rates.

Coasting/Cycle Cancellation

Coasting can be applied to cycles in which there are multiple immature follicles (>20) or high/rapidly rising serum E2 levels to reduce the risk of OHSS. This strategy refers to withholding gonadotropin therapy until serum E2 levels fall within acceptable range to proceed. Coasting is usually applied when the dominant follicle is >16 mm and the serum E2 > 3500. When E2 levels fall below 3500, controlled ovarian hyperstimulation can be started safely again. During this time, GnRH antagonists are continued to prevent premature ovulation. This method allows for larger follicles which are less FSH-dependent to continue development, while the smaller more FSH-dependent follicles undergo atresia. By decreasing the follicle count and therefore the number of granulosa cells in the smaller follicles, the risk of OHSS is lowered by reducing the factors that contribute to the development of OHSS.

The use of coasting can be safely applied to controlled hyperstimulation cycles without compromising fertilization rates, implantation rates (IR), or pregnancy rates (PR) [15]. However, Ulug et al. [16] showed lower IR and PR in patients who were coasted for 4 or more days compared with patients who were coasted for 1–3 days. Therefore, a longer duration of coasting appears to negatively impact the outcome of IVF. One disadvantage of coasting is the possibility of cycle cancellation if E2 levels do not drop after 4 days or if E2 levels drop more than 30%, due to the association with poor oocyte quality.

Ovulation Triggers

One of the major contributors to the development of OHSS is the use of hCG as a trigger to induce final in vivo oocyte maturation prior to oocyte harvesting. hCG acts by activating the LH receptor, therefore mimicking the endogenous LH surge. An important difference is the half-life

of <60 min versus >24 h for LH and hCG, respectively. The prolonged half-life of hCG results in sustained VEGF activity, thus acting as an important stimulus for OHSS. The standard dose used in the most practices is 10,000 IU; however, in patients at risk of OHSS, a reduced dose, such as 3000–5000 IU, can be used, particularly in patients with a serum E2 > 3000 pg/mL [17]. Several studies, including a randomized study by Kolibianakis et al. [18], demonstrated similar pregnancy rates using 2500 and 5000 IU compared to that of standard 10,000 IU dosing in a population of women with PCOS. Schmidt et al. [19] also found a similar proportion of mature eggs, fertilization rates, and pregnancy rates in the group of high responders using a reduced hCG dose (3300 IU vs. 5000 IU).

Another strategy that aimed at reducing the risk of OHSS is the use of gonadotropin-releasing hormone agonist to trigger the final oocyte maturation. GnRH agonists can only be employed when using a GnRH antagonist protocol due to resulting pituitary suppression seen in agonist protocols. Its mechanism is related to the more physiologic surge of gonadotropins which mimic the endogenous levels of hormones. It also serves as a luteolytic agent due to the decreased circulating half-life of the induced LH/FSH surge. This in turn prevents the secretion of vasoactive substances, such as VEGF, from the corpora lutea and reduces the risk of OHSS development.

Due to the luteolytic properties of the GnRH trigger, it is prudent to use intensified luteal support in patients anticipating a fresh embryo transfer. A Cochrane review demonstrated a lower ongoing pregnancy rate and live birth rate as well as a high rate of early miscarriage in patients using a GnRH agonist trigger [10]. However, caution must be noted in interpreting these conclusions as each of the studies used very different luteal support methods. Thus, differences in protocols may have contributed to these findings. Nevertheless, aggressive luteal support should be used when using a GnRHa trigger.

All of the aforementioned studies have demonstrated nearly complete elimination of OHSS using the GnRH agonists. A small risk remains, however, particularly in patients who are pregnant following a fresh transfer.

Calcium Infusion

Plasma renin level and renin activity have been shown to be increased in OHSS [20]. One study showed that angiotensin II levels were 100 times higher in OHSS ascites fluid compared with non-OHSS ascites fluid [21]. Higher circulating levels of angiotensin II were found to directly increase the VEGF secretion, which has emerged as one of the factors most likely involved in the pathophysiology of OHSS. Calcium infusion is thought to inhibit the renin–angiotensin system, thereby decreasing the VEGF levels. El-Khayat and Elsadek [22] recently published the results from a randomized control trial demonstrating lower rates of OHSS in high-risk women treated with calcium infusion (7% vs. 23%). Women in this study received calcium gluconate in 100 mL 0.9% saline solution on the day of oocyte retrieval and for three consecutive days after the procedure. The treatment did not appear to affect pregnancy rates.

In Vitro Maturation

In vitro maturation (IVM) is a technique involving retrieval of immature, germinal vesicle-stage oocytes in an unstimulated or minimally stimulated cycle with subsequent conversion to the metaphase II stage in vitro. The benefit of this treatment is the avoidance of a rise in serum E2 which therefore eliminates the risk of OHSS [23]. Women with an increased risk of developing OHSS, particularly those with PCOS, may benefit from this treatment option. In a retrospective study comparing 61 IVM cycles to 53 IVF-GnRH antagonist cycles, fertilization rates and embryo quality were higher among the GnRH antagonist group; however, pregnancy and delivery rates were comparable [24]. In another study comparing 107 IVM patients to 107 IVF cycles, the risk of OHSS was eliminated

with the use of IVM (compared to 11.2% in the control group) [25]. Similarly, this study did not showed the differences in PR or LBR. Ortega et al. [26] conducted a retrospective series to assess the efficiency of embryo cryopreservation after IVM in patients with PCOS. LBR per ET was 16.2%, and the cumulative LBR per patient was 21.8%.

Concerns regarding the outcomes of pregnancy achieved using IVM were addressed in a study published by Cha and colleagues [27]. One hundred and thirty-nine pregnancies using IVM from the patients with a history of PCOS were followed in a prospective observational study. The gestational age and birthweight at delivery, as well as obstetric complications, were similar to those of women treatment with conventional IVF protocol. A larger study conducted in 2012 demonstrated similar results [28]. To date, there have been several hundred births without any apparent increase in congenital anomalies.

IVM has also been studied in a non-PCOS population. In one study with 56 patients undergoing controlled ovarian stimulation, hCG was administered when the leading follicle was 12–14 mm. Approximately 76% of oocytes were mature following IVM, and patients undergoing a fresh embryo transfer carried a 46% clinical pregnancy rate [29]. IVM is an effective method to prevent OHSS, and its use has become more globally recognized, although still not adopted worldwide.

Embryo Cryopreservation

Pregnancy can often exacerbate OHSS or leads to late-onset OHSS due to the higher levels of endogenous hCG. Therefore, embryo cryopreservation allows for the resolution of supraphysiologic levels of circulating hormones, thus eliminating the risk of pregnancy associated with OHSS. Advancements in blastocyst culture have allowed time to monitor patients with developing symptoms to decide whether a "freeze-all" approach is recommended.

Fitzmaurice et al. [30] compared pregnancy outcomes with fresh and embryo transfer in patients admitted with OHSS and found no statistically significant difference between the two groups (56.5% vs. 50%, respectively). They concluded that embryo cryopreservation does not compromise the outcome of women at risk of OHSS.

A Cochrane meta-analysis included only one randomized controlled trial comparing embryo cryopreservation with IV albumin infusion and subsequent fresh embryo transfer for at-risk women, defined as E2 > 10,000 pmol/L (2724 pg/ml) and >15 oocytes or E2 > 13,000 pmol/L (3541 pg/ml) [31, 32]. This study reported no reduction in the incidence of moderate and/or severe OHSS in the group undergoing embryo cryopreservation. Further research is needed to determine whether using elective cryopreservation of embryos can reduce the risk of OHSS.

Albumin

The pathophysiology of OHSS involves third-space fluid loss due to decreased intravascular oncotic pressure. Administration of volume expanders including intravenous albumin has been postulated to maintain intravascular volume, thus preventing the downstream cascade of OHSS. In a meta-analysis including eight randomized trials comparing intravenous albumin to placebo, they showed only a marginal statistically significant decrease in the incidence of severe OHSS (OR 0.67, 95% CI 0.45–0.99) [33–38]. The same study showed there was a statistically significant decrease in severe OHSS incidence with the administration of hydroxyethyl starch (OR 0.12, 95% CI 0.04–0.40). However, safety of this substance has not been well established. Overall, no difference was seen in pregnancy rates between the groups.

Dopamine Agonists

Dopamine agonists, such as cabergoline and quinagolide, have been shown to be an effective prophylactic agent for patients receiving hCG as

a trigger for final oocyte maturation. It acts by inhibiting the VEGF receptor phosphorylation, thus decreasing the capillary permeability. In a Cochrane analysis including data from 230 women, oral cabergoline administered as 0.5 mg daily starting on the day of hCG administration or the day of oocyte retrieval and decreased the risk of OHSS development by 60% [39]. Similar pregnancy rates were seen between the groups, with no increased risk of adverse events.

GnRH Antagonist

GnRH antagonist treatment in patients down-regulated with a GnRH agonist has been proposed to reduce the risk of OHSS by decreasing the circulating E2 levels. A retrospective study by Gustofson et al. [40] found a 36% drop in E2 levels 24 h after GnRH antagonist administration from 4219.8 to 2613.7 pg/ml. This protocol involved discontinuation of the GnRH agonist and addition of HMG (75 IU) at the time of antagonist initiation. This protocol did not appear to affect oocyte recovery, oocyte maturity, or pregnancy. The use of GnRH antagonists may also be used following oocyte retrieval in patients with early-onset OHSS. This results in a decrease in E2, progesterone, as well as markers of OHSS such as haematocrit, white blood cell count, and ovarian volume.

Metformin

Metformin is an insulin-sensitizing agent that suppresses the insulin levels and decreases the excessive ovarian production of androgens in women with PCOS. By decreasing the ovarian theca cell production, it is thought to improve ovulation and pregnancy rates in this patient population [41–43]. A recent summary of the previous Cochrane review pooled data from 9 randomized controlled studies and found that metformin increased clinical pregnancy rates (OR 1.52, 95% CI 1.07–2.15), while significantly decreasing the risk of OHSS (OR 0.29, 95% CI 0.18–0.49) [44]. However, there was no clear benefit in live birth rates, warranting further investigation.

Conclusion

In conclusion, several strategies have proven successful in reducing the risk of OHSS. Beginning with identification of at-risk patients, interventions such as the use of antagonist protocols, agonist triggers, and dopamine agonists can be used to prevent or reduce the risk of severe OHSS. It is important to note that none of these strategies can completely eliminate the risk of OHSS, and thus, it is the responsibility of the clinician to take a multifaceted approach to prevent this iatrogenic complication of gonadotropin ovarian stimulation.

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