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REVIEW ARTICLE

Preventive Strategies of Ovarian Hyperstimulation Syndrome

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Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication of ovarian stimulation with gonadotropins. Although great progress has been made over the past 30 years in optimizing IVF ovarian stimulation protocols, the prevention of the unintended complication of OHSS remains a significant challenge. Several approaches have been proposed for preventing OHSS, including identification of risk factors, individualized ovarian stimulation protocols, judicious administration of gonadotropins, and careful monitoring of follicular development and serum estradiol level. Current preventive management of OHSS includes coasting, GnRH agonist ovulatory trigger, avoiding embryo transfer and embryo cryopreservation, *in vitro* maturation, albumin infusion, metformin and GnRH antagonist. Using a combination of these strategies, the incidence of OHSS can be significantly reduced. However, none of the above strategies is universally successful. Improvements in predictive tests of ovarian reserve could reduce the incidence of OHSS. Further research is needed to develop predictors of OHSS that can be used in the clinical setting. All the currently available preventive measures mentioned above have reduced but not totally eliminated the incidence of OHSS. To some degree, the occurrence of OHSS is dependent on the aggressiveness of stimulation protocols rather than the intervention. Indeed, large prospective randomized trials are needed to further assess the available strategies for avoiding this most serious syndrome.

1. Introduction

Since the birth of Louise Brown, the world's first baby born using *in vitro* fertilization (IVF), in 1978, several million babies have been born using IVF and other assisted reproductive technologies (ART).[1] Following the introduction of controlled ovarian stimulation (COS) protocols using gonadotropins, tremendous improvements in IVF success have been achieved, including optimizing COS protocols, improving prediction of response, and obtaining good quality oocytes and embryos, while maximizing implantation and pregnancy rates. In fact, pregnancy and live birth rates following IVF treatment exceed the natural conception rate in fertile couples.[2,3] However, the high success rates of IVF are achieved at the expense of requiring daily injections of gonadotropins, frequent ultrasound monitoring, and high cost and side effects of the medications. A complication that occurs almost exclusively with the use of gonadotropin stimulation is ovarian hyperstimulation syndrome (OHSS).[4]

The overall incidence of OHSS is estimated to be in the range of 1–10%.[5] Approximately 0.5–4% of patients develop severe OHSS.[4] At the Cornell Center for

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Reproductive Medicine and Infertility (CRMI), in a review of 5409 cycles from July 1997 to December 2000, there were 22 cases of mild and moderate OHSS and only three cases of severe OHSS requiring hospitalization. The overall incidence of OHSS was 0.4%, and the incidence of severe OHSS was 0.0005% of cycles.[6]

OHSS is an iatrogenic medical complication of ovarian stimulation with gonadotropins arising as a consequence of the exposure of multiple ovarian follicles to human chorionic gonadotropin (hCG). The fundamental physiologic changes observed in OHSS are related to vascular hyperpermeability secondary to the elaboration of hyperpermeability factors, principally vascular endothelial growth factor (VEGF), from the overstimulated enlarged ovaries. The resulting transudation of protein-rich fluid from the intravascular to the extravascular compartment can lead to hemoconcentration, electrolyte imbalance, and hepatic and renal dysfunction associated with life-threatening complications in severe cases. These include pleural or pericardial effusion, adult respiratory distress syndrome, thromboembolic events, myocardial or cerebral infarctions, and even death.[7–11]

The objective of this paper is to review the current preventive strategies of OHSS.

2. Predictive Factors for OHSS

Improvements in predictive tests of ovarian reserve could reduce the incidence of OHSS.[12] Predictive factors of ovarian response include patient demographics (such as age, race, weight, and body mass index), and endocrine values, including basal follicle-stimulating hormone (FSH), inhibin B, anti-Mullerian hormone (AMH), and estradiol (E_2) levels.[13–17] Ultrasonographic assessments of the ovary, including antral follicle count (AFC), ovarian volume and ovarian blood flow, have also been extensively evaluated.[18] Less commonly used dynamic tests include clomiphene citrate challenge testing, gonadotropin agonist testing, and exogenous FSH ovarian test.[19] FSH, AFC and AMH are the most commonly used predictors of ovarian response.[20–24]

A number of strategies to predict OHSS have been proposed and evaluated.[6] The most commonly used predictor of OHSS is serum E_2 level. High absolute level (> 3000 pg/mL) or rapidly rising level in the presence of multiple follicles are two indications for intervention in preventing OHSS. An E_2 level on day 9 of the menstrual cycle of > 800 pg/mL has also been reported to be an increased risk for OHSS.[25]

AMH has been evaluated as potential predictors of OHSS.[26,27] AMH has been shown to positively correlate with AFC and the number of oocytes retrieved,[28,29] and is known to be cycle-independent.[30] The levels are shown to be consistent throughout cycle.[31] Lee et al evaluated AMH and serum E_2 by means of receiver operating characteristic curve analysis in patients undergoing agonist IVF protocols and demonstrated that basal AMH and serum E_2 on the day of hCG administration are the two most reliable predictors of OHSS.[27] Using a cut-off value for AMH of > 3.36 ng/mL, the sensitivity was 90.5% and the specificity was 81.3%.

VEGF, a nonsteroidal marker of ovarian response,[32] has been investigated extensively as a potential predictor of OHSS. Wang et al demonstrated that OHSS was mediated through hCG upregulation of VEGF by luteinized granulosa cells.[33] VEGF level was shown to be correlated with interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α) levels.[34] Subsequently, Chen et al suggested that follicular fluid IL-6 concentrations and serum IL-8 concentration on the day of embryo transfer were early predictors of OHSS.[35,36]

Involvement of the renal renin-angiotensin system in the pathogenesis of OHSS has also been described. In fact, plasma renin activity has been proposed as a possible predictor of OHSS.[37]

Recently, Moos et al evaluated the predictive value of follicular and serum concentrations of inhibin A and inhibin B.[38] The samples were collected at the time of retrieval. No significant differences in serum and follicular inhibin A and B levels were found between high and low responders and among those with mild, moderate and severe OHSS.

At present, however, there are no reliable serum markers that can reliably predict OHSS.

3. Strategies for Preventing OHSS

Primary prevention of OHSS involves identification of risk factors, individualized ovarian stimulation protocols, judicious administration of gonadotropins, and careful monitoring of follicular development and serum E_2 level.[6]

3.1. Identification of patients at risk

Known risk factors for OHSS include young age, lean body weight, high gonadotropin dose, high absolute level (> 3000 pg/mL) or rapidly rising E_2 levels, and past history of OHSS. Women with polycystic ovaries (PCO) seen on ultrasound, irrespective of having other clinical features of polycystic ovary syndrome (PCOS), are at greater risk of developing OHSS.[5,39] OHSS incidence has been reported to be as high as 30% in patients with PCOS.[9,40,41] In a review of 1302 patients undergoing IVF over a 1-year period, eight patients developed severe OHSS (prevalence of 0.6%); five had ultrasonically diagnosed PCO.[4] Similarly, Engmann et al compared the ovarian response of 97 patients with PCO undergoing COS to that of 332 patients with normal ovaries. In the PCO group, nine patients developed moderate OHSS and one had severe OHSS, while only one patient in

the normal ovaries group developed OHSS.[39] In fact, PCOS patients compared to non-PCOS patients had significantly higher serum E_2 levels on the day of hCG administration and were 10 times more likely to develop moderate-to-severe OHSS despite receiving significantly less human menopausal gonadotropin (hMG).[5]

3.2. Ovarian stimulation protocols

At CRMI, a patient-centered approach is taken in the management of patients undergoing IVF. COS protocols are personalized based on patient characteristics. The dose of gonadotropin is determined based on age, body mass index, AFC, day 3 FSH and E_2, previous response, and more recently AMH level. The aim of the COS protocol is to obtain 5–15 oocytes.

A COS protocol that is applicable to patients with risk factors for OHSS is the oral contraceptive (OCP)-gonadotropin-releasing hormone (GnRH) agonist dual suppression protocol.[42] Patients are pretreated with OCP for 28 days. Leuprolide acetate (Lupron; TAP Pharmaceutical Co., Raritan, NJ, USA) 1 mg is started on day 21, overlapping the OCP for 7 days. On the third day of OCP withdrawal bleeding, a low dose of hMG or recombinant FSH (150 IU) is started and leuprolide acetate is reduced to 0.5 mg/day. Step-down gonadotropin adjustment is usually made. In most patients, gonadotropin dose is reduced by 50% during the course of stimulation. Some patients are started on a very low dose. Gonadotropin dose is gradually increased until the follicles reach 12 mm in diameter and then is reduced in step-down fashion. In a retrospective review of 99 cycles in high responders, eight patients developed mild-to-moderate OHSS.[42] There was no case of severe OHSS.

Oocyte donors are at greater risk of developing OHSS given their younger age and high AFC.[43] Maxwell et al reviewed the complications in 587 oocyte donors who underwent 973 cycles of OCP-GnRH agonist dual suppression protocol and 886 retrieval procedures in our center.[44] There was only one case of moderate OHSS requiring admission to hospital for observation, intravenous hydration, and prophylactic subcutaneous heparin. No paracentesis or other interventions were required.

The introduction of GnRH antagonist for ART has simplified COS protocols, reducing the duration of stimulation and the number of injections without sacrificing pregnancy rates.[45] The use of GnRH antagonist in ART cycles has been shown to decrease the incidence of OHSS compared to GnRH agonists.[46–49] An advantage of mid-follicular phase antagonist suppression is the possibility of using GnRH agonists to induce a luteinizing hormone (LH) surge, thus avoiding the use of hCG. Indeed, for the past 2 years, the first-line ovarian stimulation approach for patients at risk of OHSS has been the omission of GnRH agonist downregulation and utilization of GnRH antagonists when the leading follicle reaches 12–13 mm in diameter while E_2 levels exceed 300 pg/mL. The antagonist is usually administered each evening until the day of ovulatory trigger.

3.3. Adjustment of FSH starting dose

Once a gonadotropin threshold is established, and E_2 levels reach 250–300 pg/mL while several follicles measuring 11–12 mm in average diameter are observed on ultrasound, we begin to reduce the dose of gonadotropins in a step-down manner.[50] This step-down protocol appears more physiological, allowing the larger follicles to continue to develop in a relatively lower gonadotropin milieu while starving the smaller follicles, thus reducing the granulosa mass concentration of the smaller follicles.[51]

3.4. Coasting and cycle cancellation

In the presence of high or rapidly rising serum E_2 level (>3000 pg/mL) and multiple immature follicles (>20), a commonly applied strategy to prevent OHSS is coasting.[6,52] This strategy involves withdrawal of gonadotropins while the GnRH agonist and/or antagonist treatment is continued.[46]

By reducing or withholding FSH stimulation of granulosa cells, coasting reduces the growth of FSH-dependent small and intermediate size follicles with minimal effects on the growth of the larger follicles. The number of granulosa cells available for luteinization is also significantly reduced.[53] Thus, the effects of coasting may be related to the resulting apoptosis of granulosa cells in the smaller follicles, ultimately resulting in reduction of granulosa cell mass and lowering the subsequent elaboration of hyperpermeability factors secondary to hCG exposure.[54]

We prefer to commence coasting when the lead follicle reaches 14–15 mm.[50] This approach is also known as late-onset coasting. When coasting is initiated before the follicles reach 14 mm in diameter, an abrupt arrest in follicular development and a rapid decline in plasma E_2 may occur and compromise oocyte quality.

A disadvantage of coasting is the risk of cycle cancellation. hCG injection is delayed until E_2 level decreases to less than 3000 pg/mL. However, the cycle is cancelled if E_2 concentration drops by more than 30% or if the patient is coasted for longer than 4 days. The oocyte quality is usually poor under these circumstances.[51] It has also been shown that coasting for longer than 4 days resulted in significantly lowered implantation and pregnancy rates.[51,55,56]

Coasting for less than 4 days does not appear to negatively affect the number of oocytes retrieved, embryo quality, and embryo implantation and clinical pregnancy rates.[6,53,54] In a review of 124 cycles requiring coasting in our center, there was one case of OHSS.[6] The cycle cancellation rate was 35%. The live birth rates per transfer were similar when comparing patients who

were coasted for 1, 2, 3 and 4 days (69% *vs.* 50% *vs.* 46% *vs.* 71%, respectively).

In some patients undergoing GnRH agonist stimulation protocols, E_2 may continue to rise despite withdrawal of gonadotropin. Recently, Ho Yuen et al demonstrated that withdrawal of both gonadotropins and GnRH agonists dramatically reduced E_2 level within 24 hours without affecting oocyte retrieval, fertilization, embryo transfer and pregnancy rates.[57]

A qualitative review of 11 retrospective studies and one prospective randomized controlled trial found that coasting does not eliminate the risk of OHSS but may reduce its incidence in high responders.[58] A Cochrane meta-analysis found only one suitable prospective randomized controlled trial comparing coasting to early unilateral follicular aspiration.[59] The authors concluded that there is insufficient evidence to demonstrate that coasting is an effective strategy for preventing OHSS.[60]

3.5. Reduced hCG dose

The use of hCG for triggering ovulation and maintaining luteal support is known to increase the risk of OHSS.[4] Endogenous production of hCG by an early pregnancy can also exacerbate OHSS. Reducing the dose of hCG for triggering ovulation from the standard 10,000 IU to 3000–5000 IU in patients with serum E_2 level > 2000 pg/mL is another commonly applied strategy.[6]

We have utilized the following paradigm for tailoring hCG dosage: patients with E_2 level between 1500 pg/mL and 2500 pg/mL receive 5000 IU of hCG. hCG dose is reduced to 4000 IU in patients with E_2 level between 2500 pg/mL and 3000 pg/mL. The decision to administer hCG is individualized in patients with E_2 level of 3000 pg/mL hCG is withheld if E_2 significantly exceeds 3000 pg/mL or if the patient has more than 12 follicles and complains of bloating. Alternatively, if the patient has fewer than six follicles and is completely asymptomatic, a reduced dose of hCG of 3300 IU may be administered.

3.6. GnRH agonist trigger

One of the most important advantages of using GnRH antagonist for mid- to late-follicular endogenous LH surge suppression is the ability to utilize the GnRH agonist as the ovulatory trigger in patients at risk for OHSS. Indeed, the use of GnRH agonists (or recombinant LH) for triggering ovulation has virtually eliminated the risk of OHSS.[47,61–63]

The mechanisms of GnRH agonist in the prevention of OHSS is presumably related to the shorter half-life of the resulting endogenous LH surge and withdrawal of LH support for the corpora lutea, resulting in early luteolysis.[64] GnRH agonist remains in circulation for less than 24 hours and has very little luteolytic effect.[65] In contrast, serum hCG levels remain high in the serum for 7–10 days following intramuscular injection.

In a prospective randomized controlled trial comparing the use of GnRH agonist in the form of 0.2 mg triptorelin and 250 μg of recombinant hCG in 100 oocyte donors,[66] the incidence of OHSS was 16% in recombinant hCG groups versus none in the triptorelin group. The clinical pregnancy and implantation rates were comparable between the two groups (52% *vs.* 58% and 30% *vs.* 27%, respectively).

In a prospective randomized controlled trial comparing OCP-GnRH agonist dual suppression versus GnRH antagonist with 1 mg leuprolide acetate for ovulation trigger, the incidence of severe OHSS was 0% in the GnRH antagonist with leuprolide trigger protocol compared to 17% in the OCP-GnRH agonist dual suppression protocol.[67] The ongoing pregnancy rates were similar between the two treatment protocols (53% *vs.* 48%).

A meta-analysis by Griesinger et al found that GnRH agonist triggering appears to be associated with a reduction in the incidence of mild and moderate OHSS.[68] Among 1924 patients at risk of OHSS, there was only one case of OHSS in a pregnant patient. However, there is limited evidence to demonstrate the use of GnRH agonist trigger in preventing severe OHSS.[68] The same meta-analysis also showed that the use of GnRH agonist for ovulation trigger resulted in similar oocyte yield, fertilization, and embryo quality.

There are drawbacks to using GnRH agonist as the ovulatory trigger. GnRH agonist may not be effective in patients with overly suppressed LH secretion. Moreover, the use of GnRH agonist for ovulation trigger appears to be associated with lower clinical and ongoing pregnancy rates and an increase in pregnancy loss.[49,68,69] The above observations are believed to be related to luteal defect and impaired steroid production following administration of GnRH agonist.[65,70] Beckers et al compared serum progesterone and E_2 levels in the luteal phase following administration of hCG and GnRH agonist, and found the progesterone and E_2 levels to be significantly lower following GnRH agonist injection.[70]

In view of the observed luteolysis and poor steroidal production post GnRH agonist trigger, it is critical to provide luteal support for these patients. This can be achieved by the administration of daily E_2 and progesterone, and post-ovulatory low hCG doses (1500 IU), or by multiple GnRH agonist or recombinant LH administration. Engmann et al reported the use of 50 mg of intramuscular progesterone and alternating day application of 0.1 mg E_2 patch for luteal support.[67] Patients were monitored on a weekly basis in order to maintain serum progesterone above 20 ng/mL and serum E_2 level above 200 pg/mL.[67] Recently, Humaidan et al suggested using 1500 U hCG as luteal support.[71,72]

3.7. Cryopreservation of embryos

It is known that the endogenous rise in hCG associated with early gestation can exacerbate OHSS or lead to

late-onset OHSS.[73] Retrieval of oocytes followed by cryopreservation of the resultant embryos allows resolution of early OHSS and eliminates the risk of pregnancy associated with OHSS. Following transfer of the frozen-thawed embryos, the cumulative live birth rate per patient has been reported to be as high as 82%.[54,74–76]

In our center, patients with E_2 levels greater than 3000 pg/mL on the day of hCG administration (or E_2 levels greater than 4000 pg/mL on the day after hCG administration) are evaluated for symptoms and signs of OHSS on the third and, if necessary, on the fifth day following oocyte retrieval. The evaluation includes a complete physical examination, measurement of waist circumference, weight, pelvic ultrasound for ovarian size and presence of ascites, blood evaluation of hematocrit, liver enzymes and kidney function tests. Patients with findings compatible with increased risk of OHSS, especially if persistent or worsening on day 5 post retrieval, do not undergo embryo transfer and all embryos are cryopreserved. In a retrospective analysis of 42 PCO patients using GnRH agonist for triggering ovulation followed by embryo cryopreservation, all patients completed the treatment cycle without cycle cancellation, coasting, or any case of OHSS.[77] A 33% clinical pregnancy rate was achieved following frozen embryo transfer.

Two recent retrospective studies compared embryo cryopreservation to coasting for the prevention of OHSS.[54,76] The decisions to coast versus to cryopreserve were made on an individualized basis. In both studies, embryos were cryopreserved at the 2PN stage. The criteria for coasting and hCG administration differed. In the study by Gera et al, the indication for coasting was an E_2 level greater than 2500 pg/mL with more than 30 small developing follicles.[54] Huddleston et al identified patients with E_2 levels greater than 3000 pg/mL; hCG was administered when E_2 levels fell to less than 4000 pg/mL.[76] Gera et al reported that the overall incidence of OHSS was higher following embryo cryopreservation compared to coasting (41% *vs.* 0%). In contrast, Huddleston et al found that the incidences of hospitalization for OHSS were comparable between the groups (6.8% *vs.* 9.4%). Both strategies were associated with comparable live birth and cumulative pregnancy rates, although Huddleston et al found embryo cryopreservation to be associated with reduced implantation rates (14.5% *vs.* 26.5%).

Little is known about the combined effect of coasting and embryo cryopreservation on the incidence of OHSS and pregnancy outcome. In a review of eight patients at CRMI from 1995 to 1999, none of the patients developed OHSS.[6] The delivery rate per transfer was 12.5%.

A Cochrane meta-analysis identified two prospective randomized controlled trials[78,79] and found insufficient evidence to demonstrate that embryo cryopreservation is an effective strategy for preventing OHSS.[80] Compared to fresh embryo transfer and intravenous albumin administration, embryo cryopreservation did not reduce the incidence of moderate and/or severe OHSS.[78,79] Further prospective randomized controlled trials are required to evaluate the efficacy of embryo cryopreservation in the prevention of OHSS.

3.8. *In vitro* maturation

An effective yet underutilized strategy to prevent OHSS is *in vitro* maturation (IVM) of oocytes. In anovulatory patients, namely those with PCOS, immature germinal vesicle stage oocyte retrieval without any ovarian stimulation followed by IVM to metaphase-II stage represents an attractive strategy to eliminate the development of OHSS.[81] In ovulatory women with normal ovaries, the combination of natural cycle IVF with retrieval of immature oocytes followed by IVM can similarly reduce the risk of OHSS.[82]

An important benefit of IVM treatment in patients with a history of OHSS is the avoidance of a rise in serum E_2 level. In IVM treatment cycles, the mean E_2 level post-hCG injection has been shown to be within physiological range.[83]

There is no published study looking at the use of IVM in patients with a history of OHSS. However, in a case-control study comparing 107 IVM and 107 IVF cycles in women with PCOS, there were 12 cases (11.2%) of moderate or severe OHSS in IVF patients compared with none in the IVM group. There were no significant differences in pregnancy and live birth rates per retrieval (26.2% *vs.* 38.3% and 15.9% *vs.* 26.2%, respectively).[84] At McGill University, over 1000 cycles of conventional IVM or natural cycle IVF combined with IVM have been performed without any case of OHSS.[81]

IVM has also been applied as a strategy to prevent OHSS in patients undergoing controlled ovarian hyperstimulation. In 56 patients with high risk of OHSS during controlled ovarian hyperstimulation cycle, hCG was given when the leading follicle reached 12–14 mm in diameter.[85] Following IVM, 76% of oocytes matured. All patients underwent fresh embryo transfers, resulting in a clinical pregnancy rate of 46%. There were no severe cases of OHSS.

The use of IVM and natural cycle IVF combined with IVM has resulted in clinical pregnancy rates that are comparable to those obtained with conventional IVF. In women under 40 years of age, the clinical pregnancy rates were 30–40%.[81] Although the clinical pregnancy and live birth rates were lower than those achieved by IVF at some centers, the efficacy of IVM is comparable to the overall clinical pregnancy and live birth rates following IVF reported by Centers for Disease Control and Prevention/The Society for Assisted Reproductive Technology, European IVF Monitoring, and the Canadian IVF Registry.[86–88] The obstetric and perinatal outcomes of IVM pregnancies also appear to be similar to those conceived from IVF/intracytoplasmic sperm injection

(ICSI) or spontaneous conceptions.[89–91] To date, several hundred healthy infants have been born without apparent increased risk of fetal abnormality.[92]

Therefore, immature oocyte retrieval followed by IVM represents an attractive alternative to cycle cancellation, coasting, or embryo cryopreservation. At present, IVM has become an accepted ART treatment in many countries, including Canada, Korea, Sweden, Norway, and Finland.[93] IVM is gaining wider acceptance worldwide.[94,95]

3.9. Other preventive methods

Less commonly applied strategies include intravenous infusion of albumin,[78,96] metformin, dopamine agonist, cabergoline,[97–99] and GnRH antagonist administration during coasting and post-oocyte retrieval.[100–103]

3.9.1. Intravenous albumin infusion

Prophylactic administration of albumin during or following oocyte retrieval is believed to reduce third space fluid loss by maintaining intravascular oncotic pressure and minimizing capillary permeability.[9] This strategy involves intravenous administration of 50 g of human albumin diluted in 500 mL of sodium chloride 0.9% at the time of oocyte retrieval. Several prospective controlled trials have been performed to evaluate the efficacy of this intervention, demonstrating mixed results.[78,104–107] In 2002, a Cochrane meta-analysis identified seven randomized controlled trials; five met the inclusion criteria.[104,106,108–110] The authors concluded that intravenous albumin infusion resulted in a significant reduction in severe OHSS [odds ratio, 0.28; 95% confidence interval (CI), 0.11–0.73].[111] The relative risk was 0.35 (95% CI, 0.14–0.87), and absolute risk reduction was 5.5. In 2003, Bellver et al reported the largest prospective study comparing 40 g of human albumin infusion versus no treatment following oocyte retrieval in 976 patients.[112] The authors concluded that albumin infusion is not useful in the prevention of moderate and severe OHSS.[112] More recently, a small double-blinded randomized controlled trial comparing 10 g of human albumin infusion versus placebo also failed to demonstrate any protective benefit of this treatment strategy.[113]

3.9.2. Metformin

Women with PCO and PCOS are at greater risk of developing OHSS.[5,39] Metformin suppresses insulin levels and decreases ovarian theca cell androgen production, resulting in improved ovulatory and pregnancy rates.[114–116]

In a systematic review by Moll et al on metformin treatment during IVF cycle, metformin treatment led to fewer cases of OHSS (relative risk, 0.33; 95% CI, 0.13–0.80).[117] More recently, a Cochrane meta-analysis evaluated the efficacy of metformin treatment in women with PCOS undergoing IVF or ICSI cycles.[118] Five trials met the inclusion criteria.[119–123] The authors concluded that metformin treatment during IVF and ICSI cycles in women with PCOS was associated with a significant reduction in the risk of OHSS (5.7% *vs.* 21.2%).[118] The pooled odds ratio was 0.27 (95% CI, 0.16–0.47).

3.9.3. Dopamine agonist

The use of dopamine agonist, cabergoline, has been evaluated as a novel preventive treatment of OHSS. Cabergoline binds to VEGF receptor-2, leading to decreased capillary permeability.[97] In a prospective randomized double-blinded controlled trial involving 69 patients who were at risk of developing OHSS, 37 patients received an 8-day course of 0.5 mg cabergoline starting on the day of hCG administration.[98] Hematocrit, hemoglobin, and ascites were significantly reduced following 4 days of treatment. The incidence of moderate OHSS was also significantly lower than that observed in the placebo group (20.0% *vs.* 43.8%). However, no impact on late-onset severe OHSS was observed. More recently, in a prospective randomized controlled trial involving 166 patients with E_2 concentrations above 4000 pg/mL on the day of hCG administration, Carizza et al evaluated the preventive effect of intravenous human albumin infusion on the day of oocyte retrieval followed by 21 days of treatment with 0.5 mg oral cabergoline beginning on the day after oocyte retrieval.[124] Compared to placebo, the protocol of intravenous albumin and cabergoline resulted in a significant reduction in early-onset OHSS (0% *vs.* 15%). However, the incidences of late-onset OHSS were similar between the treatment and placebo groups (10.8% *vs.* 3.8%).

Cabergoline may also be an effective treatment for OHSS. In a small case series of four patients with OHSS, Rollene et al reported that administration of a 7-day course of 0.5 mg cabergoline and two daily doses of GnRH antagonist following oocyte retrieval diminished the severity and duration of OHSS.[99]

3.9.4. GnRH antagonist administration

Administration of GnRH antagonist following withdrawal of GnRH agonist has been proposed as a novel strategy of OHSS prevention in patients undergoing GnRH agonist COS protocol.[100] The treatment protocol involves discontinuation of GnRH agonist followed by daily GnRH antagonist while continuing low dose hMG (75 IU) until the day of hCG administration. Ten thousand IU of hCG was given when the E_2 concentration fell to below 3000 pg/mL.[101] The hypothesis is that the E_2 concentration could be rapidly reduced to a safe level following the administration of GnRH antagonist. The administration of low dose hMG allows the granulosa cells to be continuously exposed to FSH, thus maintaining follicular development without adversely affecting the quality of the oocytes and subsequent embryo development.

In a prospective randomized controlled trial comparing GnRH antagonist protocol to coasting, GnRH antagonist/hMG protocol resulted in significantly more oocytes, higher quality embryos, and reduced the time interval to hCG administration.[101] The pregnancy rates were comparable between the two groups. There were no cases of OHSS in either group.

The administration of GnRH antagonist following oocyte retrieval has been reported to be an effective treatment option for patients with early-onset severe OHSS. Bonilla-Musoles et al reported that the administration of a high dose of GnRH antagonist (3 mg) resulted in a rapid drop in E_2 concentration and ascites in six patients with early-onset severe OHSS.[125] Similarly, Lainas et al reported marked decreases in hematocrit, white blood cell count, E_2, progesterone, ovarian volume and ascites fluid in patients with OHSS following 1-week administration of GnRH antagonists.[102,103] Larger prospective controlled trials are required to confirm the efficacy of GnRH antagonist in these settings.

4. Conclusions

The primary approach in the prevention of OHSS involves identification of risk factors, individualized ovarian stimulation protocols, judicious administration of gonadotropins, and careful monitoring of follicular development and serum E_2 level. Using a combination of the strategies discussed, the incidence of OHSS can be significantly reduced. However, none of the strategies is universally successful. Further research is needed to identify reliable predictors of OHSS that can be used in clinical settings. The efficacies of coasting, embryo cryopreservation, IVM, albumin infusion, metformin, and GnRH antagonist administration need to be confirmed by further prospective randomized controlled trials. GnRH agonist triggers appear to be the most promising approach in women undergoing stimulation with GnRH antagonist protocols.

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