Ovarian hyperstimulation syndrome (OHSS) is a potential complication of ovarian stimulation in the treatment of infertility. Severe forms of OHSS appear in 0.5–5.0% of in vitro fertilization (IVF) cycles. A critical condition develops with massive ascites or pleural effusion, dyspnea, hemoconcentration and oliguria that can be life-threatening. The underlying cause is an increase in the capillary permeability of the ovaries and mesothelial surfaces with extravasation of protein-rich fluid, which in turn causes hypovolemia, reduced organ perfusion and the risk of thromboembolism. Several angiogenic and vasoactive cytokines, including vascular endothelial growth factor (VEGF), interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α) and angiotensin II, produced from multiple corpora lutea were attributed to pathogenetic factors. A better understanding of the underlying pathophysiologic and signal mechanisms would be helpful for prevention and treatment.

Human Chorionic Gonadotropin is a Contributing Inducing Factor of OHSS

The development of OHSS following ovarian stimulation with gonadotropins is mainly associated with the administration of human chorionic gonadotropin (hCG) as the syndrome rarely develops if it is withheld. In addition, OHSS becomes more severe after pregnancy occurs. VEGF has been found to be an important mediator of OHSS. Expressions of VEGF mRNA and secretion of VEGF protein are positively regulated by hCG in granulosa lutein cells. VEGF stimulates new blood vessel development and vascular hyperpermeability by acting through VEGF receptor 2 (VEGFR-2) on the endothelial cells. However, the signal pathway of hCG-induced VEGF secretion is still unclear and deserves further investigation.

Other Factors and Vasoactive Cytokines May Contribute to OHSS

Lysosphatidic acid (LPA) has been detected to exist at considerable amounts in the follicular fluid of preovulatory follicles. Recently, LPA has been found to be an important regulator of IL-8 and IL-6 in granulosa lutein cells. LPA induces IL-8 and IL-6 expression through LPA receptors, mitogen-activated protein kinase and nuclear factor-κB dependent pathways. LPA-induced IL-8 and IL-6 increase the permeability of the endothelial monolayer. However, the signal pathways of IL-8 and IL-6 in endothelial cells leading to vascular hyperpermeability in OHSS remain elusive. In addition to VEGF, the relative effects of IL-8,
IL-6, TNF-α and angiotensin II that contribute to OHSS are unclear and need further clarification.

Prevention of OHSS

Coasting with cessation of gonadotropin has been widely adopted to reduce OHSS in high-risk conditions with massive follicular growth. However, prolonged coasting has the drawback of a reduced pregnancy rate. Therefore, what constitutes an optimal strategy for coasting deserves further study. Prophylactic albumin could be helpful in preventing OHSS in high-risk patients. However, it does not completely eliminate severe OHSS. Luteal support with progesterone and estradiol, rather than hCG supplements, reduces the risk of OHSS. Adoption of the strategy of blastocyst transfer may permit more time in which the possibility of OHSS can be evaluated. Elective cryopreservation of all embryos for postponement of transfer can prevent the occurrence of late OHSS from pregnancy. For high-risk patients, mild ovarian stimulation with the gonadotropin and gonadotropin-releasing hormone (GnRH) antagonist protocol may prevent OHSS.

hCG is Currently Used as Standard Method for Triggering Oocyte Maturation, But It Increases OHSS Risk

hCG has been used as a substitute luteinizing hormone (LH) surge because it has structural homology and results in similar action. Both LH and hCG are heterodimeric glycoproteins with identical α subunits and different β subunits. They can induce ovulation and luteinization as well as support luteal cells. The major difference between the two hormones is the pharmacokinetics of clearance. Compared with LH, hCG has a slower plasma metabolic clearance. The calculated half-life of hCG was 2.3 days and that of LH was 3–5 hours. hCG has sustained luteotropic action because of its prolonged circulating half-life that may predispose to OHSS. Recently, Nargund et al reported that reduction of hCG dosage to 2500 IU for triggering oocyte maturation decreased the incidence of OHSS in high-risk patients.

Use of LH for the Replacement of hCG in Triggering Oocyte Maturation

The development of recombinant LH (rLH) may offer an opportunity to replace hCG. The European rLH study group performed a prospective and comparative study on the effective dose of rLH required to induce oocyte maturation and luteinization in patients undergoing IVF. A dose of 15,000–30,000 IU rLH compared with 5000 IU hCG resulted in a similar number of oocytes, embryos and pregnancies. The use of rLH achieved a significant reduction in OHSS compared with hCG. More effort should be made to use rLH as an alternative to hCG as the standard method for induction of oocyte maturation and OHSS prevention.

Use of GnRH Agonist to Induce LH Surge in Non-agonist or Antagonist Cycles

GnRH agonist can stimulate the release of LH and follicle stimulating hormone. It has been used to induce endogenous LH surge in ovulation induction. However, the pregnancy rate was lower than that with the use of hCG. This disappointing result has been attributed to a luteolytic effect caused by the agonist. The introduction of GnRH antagonist protocols has resulted in renewed interest in the use of GnRH agonist to trigger ovulation. Recently, a prospective randomized controlled study of IVF patients found no differences in the number of mature oocytes, fertilization rates, embryo development and implantation rates between the GnRH agonist and hCG groups. The risk of OHSS was significantly reduced in the former group. The use of GnRH agonist to induce final oocyte maturation in the antagonist protocol with appropriate luteal support may be a good alternative to avoid OHSS and deserves further investigation.
Dopamine Agonist (Cabergoline) Inhibits VEGFR-2-mediated Vascular Hyperpermeability

The downstream signals of VEGFR-2 in endothelial cells for vascular permeability in OHSS may involve VE-cadherin and merits further delineation. It was recently found that dopamine or dopamine receptor 2 (DR-2) agonists transact inhibition of VEGFR-2 dependent vascular permeability and angiogenesis through DR-2 of endothelial cells. Gomez et al first investigated the effect of DR-2 agonist (cabergoline) on OHSS in a rat model. They found that a low dose of cabergoline reversed vascular permeability without affecting luteal angiogenesis. Alvarez et al conducted a pilot study on patients at risk of developing OHSS who were given cabergoline (0.5 mg/day) orally from the day of hCG for 9 days. They observed that ascites, hemoconcentration, vascular hyperpermeability and OHSS were significantly reduced. They further demonstrated that implantation and pregnancy outcome were not affected by cabergoline treatment. However, the case number in their series was small. In addition, angiogenesis is a fundamental step in implantation and pregnancy.

Conclusions

Fluid, electrolyte and albumin supplements or paracentesis and thoracentesis have been used as primary treatments for severe OHSS. Recent advances in prevention and treatment have significantly reduced the incidence of OHSS. Mild stimulation of the ovaries may avert the development of OHSS. The use of GnRH agonist to induce final oocyte maturation in the antagonist protocol may reduce OHSS. Coasting is effective in reducing OHSS, but what constitutes optimal timing needs further investigation. Reduction of hCG dosage for triggering oocyte maturation may diminish OHSS. The effects of cabergoline on the prevention of OHSS merit further study. In-depth study of signal pathways in luteal and implantation angiogenesis as well as vascular permeability would be helpful for appropriate targeting therapy of OHSS. The possible role of VEGF inhibitor or immunomodulators of TNF-α in the treatment of OHSS

Prevention

Strategies before oocyte retrieval
- Mild stimulation
- Coasting
- Reduction of hCG dose
- GnRH agonist for triggering ovulation
- rLH for triggering ovulation
- Cancellation of cycle

Mechanisms

Multiple corpora lutea in ovary

Endothelial cells

Hyperpermeability with fluid extravasation

Secretion of VEGF, IL-8, IL-6, TNF-α, angiotensin II, etc.

Management

Strategies after oocyte retrieval
- Albumin, fluid and electrolyte supplement
- Luteal support with progesterone and estradiol, instead of hCG supplements
- Dopamine agonist (cabergoline)
- Blastocyst transfer and sonography for ovaries and ascites
- Cryopreservation of all embryos

Figure. Mechanisms and management of ovarian hyperstimulation syndrome.
may deserve further investigation. The use of rLH for inducing oocyte maturation is imperative in the prevention of OHSS in the future. The mechanisms and management of OHSS are summarized in the Figure.

References


