TREATMENT OF OVARIAN HYPERSTIMULATION SYNDROME: NEW INSIGHTS

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SUMMARY – Ovarian hyperstimulation syndrome is the most serious iatrogenic complication resulting from ovarian stimulation. Currently there is no clear evidence of absolute efficacy for most of standard preventive and curative methods. Recent studies indicate that human chorionic gonadotropin increases vascular endothelial growth factor, vascular endothelial cadherin and vascular permeability via endothelial adherence junctions. Vascular endothelial growth factor plays a pivotal role in the pathophysiology of the condition and therefore vascular endothelial factor antagonism has been suggested for the prevention of the syndrome. Since vascular endothelial growth factor is also a physiological regulator of folliculogenesis, progesterone secretion and endometrial angiogenesis, its complete inactivation by specific blockers could produce undesirable effects interfering with early pregnancy development and therefore they cannot be used clinically. Recently, low doses of dopamine agonists (cabergoline) have been shown to counteract vascular endothelial growth factor induced vascular hyperpermeability, reducing the incidence of the syndrome by prophylactic treatment without compromising pregnancy outcome. The absence of undesirable side effects could make cabergoline an effective and safe etiologic approach for the prevention and treatment of the syndrome. A novel approach has suggested that metformin may also be helpful in the syndrome prevention in women with or without polycystic ovary disease.

Key words: Ovarian hyperstimulation syndrome – therapy; Ovulation induction – adverse effects; Ovulation induction – risk factors; Dopamine agonists

Introduction

The ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation, occurring during the luteal phase or early pregnancy. It is typically associated with the use of exogenous gonadotropins or occasionally with clomiphene citrate, and extremely rarely in a spontaneous cycle during early pregnancy. As the overall incidence of clinically relevant OHSS is up to 10% of cycles and severe forms of OHSS arise in 0.5%-5% of in vitro fertilization (IVF), it is important for all clinicians to be aware of the strategies for its prevention. Since this is a potentially life-threatening syndrome, it is unfortunate that despite increased awareness of the well-known prognostic variables OHSS may not always be prevented.

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, has emerged as one of the factors most likely to be involved in the pathophysiology of OHSS. Recent studies indicate that human chorionic gonadotropin (hCG) is the main factor that triggers OHSS and seems to be the pivotal stimulus of the syndrome because elimination of hCG will prevent the full-blown picture of the syndrome. It has been clearly demonstrated that hCG increases VEGF and its VEGF-2 recep-
tors in human granulosa-lutein cells and raises serum VEGF concentrations. VEGF acts through the VEGF receptor 2 (VEGFR-2) on the endothelial cells and it is the main mediator responsible for the prominent role in the pathologic increase of vascular permeability. Similarly, hCG and VEGF individually produce a significant increase in VE-cadherin release, which is involved in the loosening of endothelial intercellular junctions. VE-cadherin is a soluble cell adhesion molecule that may play a key role in the pathophysiology and progression of vascular hyperpermeability.

The hallmark of OHSS is an increase in capillary permeability of the ovaries and mesothelial surfaces, resulting in extravasation of protein-rich fluid into the third space, which in turn causes hypovolemia, reduced organ perfusion and the risk of thromboembolism. A critical condition develops with massive ascites or pleural effusion, dyspnea, hemoconcentration and oliguria. The manifestations of OHSS are believed to be the result of increased capillary permeability and range from mild abdominal discomfort to severe, life-threatening illness.

In the past, several preventive and curative approaches were suggested. As to date, the condition of OHSS is not yet completely understood. No known pharmacological intervention that fully prevents the development of the syndrome and no completely curative therapy has yet been detected. However, owing to recent insights into the pathophysiology of the syndrome, new proposals and strategies of prevention have been reported. OHSS continues to be among the most serious complications of ovulation induction and range from mild abdominal discomfort to severe, life-threatening illness.

Prevention

Cancelling

The oldest and the most effective method in preventing OHSS has been abandonment of the cycle, however, only 11% of physicians would consider cancelling because of high costs and tremendous effort invested by the couple. Withholding hCG and cycle cancellation was the most commonly used method of preventing OHSS, but at the expense of losing cycle with heavy psychological and financial burdens upon the patient.

Coasting

Coasting with cessation of gonadotropins until serum estradiol (E2) levels drop to a safe level has been widely adopted to reduce OHSS, however, prolonged coasting has the drawback of a reduced pregnancy rate. It is a good alternative that can be used to avoid cycle cancellation in extremely high responders to ovulation induction, who have a high risk of developing severe OHSS. Even if OHSS develops after coasting, both its incidence and severity will be diminished. Until multifactorial etiopathogenesis of OHSS is completely understood, absolute prevention will not be possible, but coasting is definitely of great benefit.

Stimulation protocols

The risk of OHSS is particularly evident when ovulation induction for IVF procedure is performed with elevated gonadotropin dosages. It is advisable to use a low starting dose of 150 IU for all patients at a possible risk of OHSS, irrespective of their age. The low-dose, step-up protocol and the step-down protocol are associated with a low risk of OHSS. The use of gonadotropin releasing hormone (GnRH) agonists, especially of a long protocol, increases the incidence of OHSS. However, the use of GnRh antagonists significantly reduce OHSS incidence at the expense of lower ongoing pregnancy rates. hCG is currently used as a standard method for triggering oocyte maturation, although it is the main factor that increases OHSS risk. Therefore, it has been suggested that a lower dose of urinary hCG (e.g., 5,000 vs. standard 10,000 IU dosage) or 250 mcg of recombinant hCG may further reduce the risk of OHSS.
Early unilateral follicular aspiration (EUFA)

In the first report, EUFA was applied in patients at risk of OHSS 12 h after hCG administration, followed by regular oocyte retrieval 36 h later. It was suggested that intra-ovarian bleeding induced by follicular aspiration of granulosa cells from one ovary would limit the production of ovarian mediators of OHSS and thus reduce the risk of developing severe OHSS. The method of post-hCG-aspiration in one ovary was described as a simple and effective method that prevented the development of OHSS. However, these data are contradictory, with results of a prospective randomized study comparing unilateral ovarian aspiration with the coasting, where neither method completely prevented the occurrence of severe OHSS.

Treatment

Albumin

A Cochrane review reported a clear benefit from prophylactic administration of albumin at the time of oocyte retrieval and it could be helpful in the prevention of severe OHSS in high-risk patients. Albumin seems to have osmotic and transport functions, drawing extracellular fluid into the circulation and binding or inactivating the vasoactive substances responsible for the pathogenesis of OHSS. However, in a recent prospective randomized study, it was found that human albumin did not seem to either prevent or reduce the incidence of severe OHSS. Without a concomitant reduction in vascular permeability, however, the effect of albumin on intravascular volume and hematocrit may be of short duration due to its diffusion into the extravascular space, exacerbating both ascites and pleural effusions.

Embryo cryopreservation

Elective transfer of a single zona-free day 5 embryo and freezing of the supernumerary embryos or cryopreservation of all embryos for postponement of transfer can prevent the occurrence of late OHSS from pregnancy. However, it does not prevent early OHSS development due to exogenous hCG administration. The management based on elective 2 pronucleate embryo cryopreservation with subsequent thaw and grow-out to blastocyst stage for transfer did not appear to compromise embryo viability or overall reproductive outcome. For these patients, immediate elective embryo cryopreservation and delay of embryo transfer by as little as 30 days allowed for satisfactory conclusion of the IVF sequence, yielding a live birth-delivery rate of 33% per initiated cycle and 43.6% per transfer.

Paracentesis

The vast majority of patients with severe OHSS had their condition successfully managed as outpatients with the use of aggressive transvaginal paracentesis. Immediately after paracentesis, characteristic hemodynamic changes occurred including decreased intra-abdominal pressure, improved venous return, and improved renal perfusion. In addition to the mechanical improvements in blood flow occurring after removal of ascites fluid, the other mechanisms by which paracentesis has been proposed to improve condition in OHSS is by direct removal of the inflammatory, vasodilatory, and angiogenic substances released by hyperstimulated ovaries.

New therapeutic approaches

Until recently, the pathophysiology of OHSS was poorly understood and it is still a complex process. Therefore, there is no standard pharmacological intervention that fully prevents the development of the syndrome and no completely curative therapy. However, since recently several observations from animal studies suggest that development of OHSS is probably mediated by increased ovarian production and secretion of vasoactive substances, with VEGF being the main candidate among them. VEGF signaling through VEGFR-2 stimulates not only new blood vessels in follicular growth, luteal function and embryo implantation, but it is also an important regulator of vascular permeability.

Natural inhibitors

It is surprising that, among women who display high parameters of ovarian response and who should therefore run the same risk of OHSS, only some develop the syndrome. This discrepancy may be related to soluble proteins that bind to VEGF. The VEGF soluble receptor-1 (sVEGFR-1) is reported to act as a modulator of VEGF bioactivity, which competes with the full-length VEGFR to bind to VEGF and...
Another molecule, alfa2-macroglobulin, a major serum-binding protein associated with tissue remodeling during ovulation and corpus luteum maintenance, is also thought to determine the availability of free VEGF to bind to VEGFR-2\(^2\). During the luteal phase, hyperstimulated patients who developed OHSS presented total and free VEGF levels significantly higher than those observed in women who had not undergone hyperstimulation, including those with a strong ovarian response. High levels of these proteins may decrease free VEGF and protect against OHSS. Women who did not develop OHSS, among whom both normal and strong responses to stimulation were observed, presented significantly higher plasma levels of natural antagonist sVEGFR-1. Although the ability of alfa2-macroglobulin to bind and inactivate VEGF is well known, its relevance in OHSS is not yet confirmed\(^2\).

**VEGFR-2 inhibitor (SU5416)**

Validation of the importance of the VEGF/VEGFR-2 pathway in OHSS comes from the findings in which development of the syndrome could be prevented by the administration of SU5416, a VEGFR-2 inhibitor, a substance that blocks VEGFR-2 phosphorylation. It was demonstrated for the first time that hCG-induced changes in vascular permeability could be prevented by interference with the VEGF/VEGFR-2 signaling pathway\(^2\). Unfortunately, SU5416 cannot be used clinically due to its side effects (thromboembolism, vomiting) and the possibility that it might interfere with early pregnancy development by blocking implantation related ovarian and uterine angiogenesis\(^2\).

**Dopamine agonists**

There is a need to pharmacologically segregate the permeability component from the angiogenic portion of the VEGF/VEGFR-2 pathway to treat this syndrome. It was recently found that dopamine (Dp) or dopamine receptor 2 (Dp-r2) agonists transacted inhibition of VEGFR-2 dependent vascular permeability and angiogenesis through Dp-r2 of endothelial cells. Administration of high doses of Dp-r2 agonists simultaneously blocks tumor related angiogenesis and vascular permeability in a mouse cancer model by interfering with VEGF/VEGFR-2 signaling. In *vitro* studies suggested that the molecular mechanism underlying this action involved internalization of VEGFR-2 induced by activation of Dp-r2. The receptor became unreachable for VEGF, and this led to a general inhibition of the VEGF/VEGFR-2 pathway, which resulted in not only decreased vascular permeability but also angiogenesis\(^2\). It is well known that doses of Dp-r2 agonists much lower than those used in the tumor model are sufficient to activate the Dp-r2 pathway, as demonstrated by the fact that they decrease prolactin secretion by the pituitary gland. Thus, low-dose Dp-r2 agonists are successfully used for the treatment of hyperprolactinemia in humans. Interestingly, at these low doses, Dp-r2 agonists do not exert antiangiogenic activity because physiological states of high level VEGFR-2-dependent vascular activity like formation of corpora lutea or pregnancy development are not affected\(^2\). Using a prolactin-supplemented OHSS rat model, it was shown that a low dose of Dp-r2 agonist cabergoline retained the ability to decrease vascular hyperpermeability without affecting angiogenesis. Cabergoline action seems to be mediated through activation of Dp-r2 because endogenous prolactin secretion, a marker of Dp-r2 activity, was consistently reduced by the drug administration. Activation of Dp-r2 is associated with changes in the VEGF/VEGFR-2 pathway, as indicated by partial blockage of VEGFR-2-specific phosphorylation site. These findings indicate that the permeability component of VEGF/VEGFR-2 pathway can be segregated from the angiogenic component by Dp-r2 agonists in a dose-dependent manner. Cabergoline blocks not only hyperpermeability in the rat OHSS model but also a similar condition in human, which can occur during infertility treatment. Owing to these findings, a new clinical application for cabergoline or a specific nontoxic treatment of OHSS has been suggested for the first time, without affecting reproductive angiogenesis\(^2\). In several recent studies, these beneficial effects were confirmed and Dp-r2 agonists were proposed as a prophylactic treatment of OHSS in women at high risk in IVF treatment cycles. The preventive dose of 0.5 mg of oral cabergoline per day for 1 to 3 weeks starting on the day of hCG administration has been suggested in most studies\(^1,4,29,30\). In a recent meta-analysis of 4 randomized trials including 570 women, there was evidence for a statistically
significant reduction in the incidence of OHSS in the cabergoline group, with an absolute risk reduction by 12%. However, there was no statistically significant evidence for a reduction in severe OHSS and no evidence for difference in the clinical pregnancy rate. It was concluded that prophylactic treatment with the dopamine agonist cabergoline reduced the incidence, but not the severity of OHSS, without compromising pregnancy outcome. In spite of these beneficial effects of the dopamine agonist cabergoline on vascular permeability without compromising implantation and pregnancy rates, this treatment would complement the ongoing progress with other procedures such as in vitro maturation and oocyte vitrification and enable physicians to predict and prevent OHSS.

Metformin

Women affected by polycystic ovary disease are a subgroup of patients at the highest risk of OHSS, with an incidence of 6% in these women compared with 1% in the general infertile population after ovulation induction. A recent meta-analysis has shown the polycystic ovary disease women treated with metformin to have a statistically significantly lower incidence of OHSS compared with the untreated group. Although the mechanism of action of metformin is unclear, it seems that the reduction of ovarian reserve, as demonstrated by the reduction of antimüllerian hormone values, and a reduced insulin dependent VEGF production, have been suggested. Moreover, a novel approach has been suggested in a recent pilot study, i.e. that metformin as a safe and inexpensive drug may also help in the prevention of OHSS development in women without polycystic ovary disease.

Conclusion

Until multifactorial etiopathogenesis of OHSS is completely understood, absolute prevention and treatment of OHSS will not be possible, and are currently based on an empirical and symptomatic approach. Due to the clear lack of efficacy for most of the standard preventive and curative measures in the past, there was an urgent need for further investigations in the pathophysiology of this syndrome. Recent observations from several studies suggest that VEGF or vascular permeability factor plays a pivotal role in increasing vascular permeability in hyperstimulated patients under the influence of hCG. Therefore, it seems that the most promising way to prevent OHSS might be hCG dose tapering or use of its alternatives to reduce VEGF production. In addition to cabergoline-mediated VEGF antagonism by Dp-2r stimulation in combination with metformin promote an effective step further in the etiologic therapeutic approach to OHSS.

References


Sažetak

LIJEČENJE Ovarijskog HIPERSTIMULACIJSKOG SINDROMA: NOVI UVIDI

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Ovarijski hiperstimulacijski sindrom je najozbiljnija jatrogena komplikacija koja nastaje nakon stimulacije jajnika. Zasad nema jasnih dokaza o apsolutnoj djelotvornosti većine standardnih i preventivnih i kurativnih metoda. Novije studije pokazuju da humani korionski gonadotropin povisuje vaskularni čimbenik rasta, vaskularni endotelni kaderin i vaskularnu propusnost na spojevima adherentnog endotela. Kako vaskularni endotelni čimbenik rasta igra ključnu ulogu u patofiziologiji sindroma, ukazuje se na onemogućavanje djelovanja vaskularnog čimbenika rasta u prevenciji bolesti. Budući da je vaskularni čimbenik rasta ujedno i fiziološki regulator folikulogeneze, stvaranja progesterona i krvnih žila endometrija, njegova bi potpuna inaktivacija specifičnim blokatorima dovela do neželjenih nuspojava koje bi ometale razvoj rane trudnoće, što onemogućuje njihovu kliničku primjenu. Odnosno se pokazalo kako niske doze agonista dopamina (kabergolin) suzbijaju pojačanu vaskularnu propusnost izazvanu vaskularnim endotelnim čimbenikom rasta, smanjujući profilaktično pojavnost sindroma bez nepovoljnog djelovanja na ishod trudnoće. Zbog izostanka nepoželjnih nuspojava kabergolin bi mogao biti djelotvoran i siguran u etiološkom pristupu te u prevenciji i liječenju sindroma. Noviji pristup ukazuje na to da primjena metformina može isto koristiti u prevenciji sindroma kod žena s policističnim jajnicima ili bez njih.

Ključne riječi: Sindrom hiperstimulacije jajnika – terapija; Indukcija ovulacije – štetni učinci; Indukcija ovulacije – čimbenici rizika; Agonisti dopamina