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Review Article

VEGF antagonist for the prevention of ovarian hyperstimulation syndrome: Current status

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ABSTRACT

Ovarian Hyperstimulation Syndrome (OHSS) an iatrogenic and potentially life-threatening complication resulting from an exaggerated response to ovulation induction with gonadotropins during assisted reproductive technologies, is a self-limiting disorder with a broad spectrum of clinical manifestations related to increased capillary permeability and fluid retention brought about by many biochemical mediators especially vascular endothelium growth factor (VEGF), playing a pivotal role in its pathophysiology. Although various strategies had been proposed and tried to prevent this serious complication none was found to be completely effective. With the current knowledge and understanding of the causative molecule i.e. VEGF in the pathogenesis of OHSS, pharmacologic tools targeting this member of the family of heparin binding proteins, seems promising. Antagonizing and blocking VEGF action by dopamine agonists especially Cabergoline has shown to be a valid alternative to overcome the changes induced by the gonadotropins. Delaying embryo transfer with embryo cryopreservation definitely reduces the incidence of OHSS but not the early OHSS. In-vitro maturation of oocytes a major breakthrough in the field of ART although totally eliminates the risk of OHSS is highly labor intensive and cannot routinely carried in all cycles. Thus the newer drugs, mainly the dopamine agonists in the light of the new pathogenic and pharmacological evidence, should definitely be considered for prevention of both early and late OHSS.

Introduction

Ovarian Hyperstimulation Syndrome (OHSS) an iatrogenic complication of controlled ovarian hyperstimulation (COH) occurs due to an exaggerated response to ovulation induction with gonadotropins especially in, in-vitro fertilization cycles (IVF) and very rarely due to ovulation induction with clomiphene citrate. OHSS is a self-limiting disorder with a broad spectrum of clinical manifestations related to increased capillary permeability and fluid retention brought about by many biochemical mediators, the most important being vascular endothelium growth factor (VEGF).[1]

OHSS may be mild, moderate, or severe depending on the various clinical, radiological and laboratory parameters but the clinical impact of the syndrome depends on the variety of symptoms caused by the development of ascites, pleural effusion, hemoconcentration, reduced renal perfusion, and thrombotic complications.

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This iatrogenic entity can although affects 12–25% of IVF cycles, severe forms of ovarian hyperstimulation syndrome (OHSS) arises in 0.5–5% of assisted reproduction treatment (ART) cycles, and in its most severest form even known to cause maternal death.[2,3] Despite being a potentially life-threatening condition, this syndrome has largely been managed expectantly and empirically until now, due to its elusive pathophysiology.

Several approaches have been proposed in the past to prevent this complication. But these measures have not shown to offer complete protection against the development of OHSS. Among the selected preventive methods, discontinuing gonadotropin therapy (coasting), withholding human chorionic gonadotropin (hCG) and intravenous albumin administration were by far the most popular choices.[4] Embryo Cryopreservation, another strategy, though useful for avoiding the late form of this syndrome due to endogenous hCG production, does not prevent early OHSS development due to exogenous hCG administration. So the search for an ideal pharmacotherapy for the prevention of this potentially deadly complication remained. With the better understanding of its pathophysiology and the pivotal role of VEGF implicated in the causation of OHSS, Cabergoline (Cb2) a dopamine agonist with its anti VEGF activity has been demonstrated to be an effective and safe drug, for the prevention of this disorder.[4]

The aim of this article is to briefly review the pathogenesis of OHSS, concentrating mainly on the causative role of vascular endothelial growth factor and the rationale for the use of cabergoline, for the prevention and treatment of this syndrome due to its role as a VEGF antagonist.

Pathophysiology of OHSS and the role of VEGF

OHSS, primarily a systemic disease results from vasoactive products released by the ovaries hyperstimulated with gonadotropins. It is more frequently seen when a strong ovarian response occurs, characterized by the development of a large number of follicles, high estradiol (E2) values and enlarged ovaries.

The mechanism postulated for this syndrome is increased vascular permeability (VP) and extravasation of fluid, which in turn causes hemoconcentration with reduced organ perfusion, alterations in blood coagulation and the resulting risk of thromboembolism, and leakage of fluid into the peritoneal cavity and lungs.[2,5] The exogenous administration of hCG which is the final step in triggering oocyte maturation, is the most important prerequisite for the development of OHSS after controlled ovarian hyperstimulation because the syndrome does not develop if hCG is withheld.[6] As hCG per se, has no vasoactive property, the angiogenic molecule, vascular endothelial growth factor (VEGF) has been implicated as the most important mediator of hCG-dependent ovarian angiogenesis. VEGF has been found to be expressed in human ovaries and it has been observed that VEGF mRNA levels increases after hCG administration in granulosa cells and the elevated levels of the secreted proteins have been detected in serum, plasma, and peritoneal fluids in women at risk or with OHSS.[7–9] VEGF stimulates new blood vessel development and vascular hyperpermeability by interacting with its VEGF receptor 2 (VEGFR-2).[10–12]

VEGF apart from being a powerful mediator of vascular permeability which is the most important characteristic of this condition; is also strongly implicated in the initiation and development of angiogenesis in the developing embryo and in adult tissues undergoing profound angiogenesis, such as cycling endometrial tissue and the luteinizing follicle. It also plays an important role in the growth and maintenance of ovarian follicles and corpus luteum by mediating neovascularisation.[6]

In addition to the exaggerated follicular angiogenesis and the increased capillary permeability mediated by VEGF in the pathogenesis of OHSS, the other pathogenetic forerunners postulated for this syndrome are: the immune system and the rennin angiotensin system (RAS).[13,14]

The immune system and the reproductive system have been found to be linked through cytokines and their receptors which in turn lead to the local and systemic effects of immune response. Pro inflammatory cytokines: interleukin-1β, IL-6, IL8 and tumor necrosis factor α have been implicated to mediate the acute phase response which leads to capillary leakage and the third space loss of OHSS.[15] Elevated serum levels of these cytokines have been found in OHSS.

The Renin-Angiotensin system (RAS) of the ovary also plays a causative role in the pathogenesis of this disorder and has been found to function independently of the renal RAS.[16] The local RAS of the ovary leads to conversion of the avascular pre ovulatory follicle into a richly vascularized corpus luteum. Ovarian follicles contain rennin in an inactive form, prorenin, which is activated at mid cycle, causing conversion of angiotensinogen to angiotensin I. This in turn is converted to angiotensin II by the angiotensin converting enzyme (ACE). Angiotensin II promotes angiogenesis, increased vascular permeability and stimulates release of prostaglandins. High rennin activity has been demonstrated in human follicular fluid and plasma from patients with OHSS. Thus ovarian RAS very similar to the action of VEGF also brings about new vessel formation and increased capillary permeability leading to ovarian enlargement and extracellular fluid sequestration a, characteristic feature of OHSS.[17]

Classification of OHSS

Although several classification systems for OHSS are in existence, but most of them are an amalgamation of the clinical, laboratory and the ultrasonological findings to categorize the severity of the disease. The most frequently utilized and popular classification system is that of Golan et al which primarily incorporates transvaginal sonography to estimate the ovarian enlargement and presence of ascitic fluid[18] (Table 1). Further modifications were subsequently brought about, refining the classification to differentiate severe and critical OHSS[19] (Table 2).

However it needs to be reiterated that OHSS is a dynamic condition with clinical symptoms and signs exhibiting a continuum. The upward and downward course of the syndrome defies any attempt at specific classification. A moderate OHSS patient may progress within hours or days to

Table 1 – Classification of OHSS.

Mild	
Grade 1	Abdominal Distension and discomfort
Grade 2	Grade 1 plus nausea, vomiting and/or diarrhea; ovaries enlarged to 5–10 cm
Moderate	
Grade 3	Features of mild OHSS plus ultrasonic evidence of ascites
Severe	
Grade 4	Features of moderate OHSS plus clinical ascites and/or hydrothorax with dyspnea
Grade 5	Grade 4 plus decreased blood volume, increased blood viscosity, hypercoagulability and diminished renal perfusion and function

a severe case. Thus clinicians have to be vigilant even when monitoring a mild or a moderate OHSS.

OHSS can also be divided into "early" and late" depending on the time of onset which helps in predicting the prognosis.[20] The manifestations occurring within 9 days after the triggering dose of hCG reflects the excessive ovarian response and the precipitating effect of exogenously administered hCG for the final follicular maturation. On the other hand OHSS presenting after this duration reflects the stimulation secondary to endogenous hCG from an early pregnancy.[20,21] Thus late OHSS is likely to last longer and of greater severity.

Drugs targeting the causative molecule

With VEGF being causative in the pathophysiology of OHSS various drugs were suggested which would block the over expression of VEGF and VEGFR-2 in the ovaries. SU5416, a compound that blocked the intracellular phosphorylation of VEGFR-2 was experimented upon in animal models but due to its side effects (thromboembolism and vomiting) and the possibility of its interference with early pregnancy development, this drug could not be employed in the clinical treatment for this syndrome.[22] Other compounds were also investigated which would affect the vascular permeability, but they had to be, without the undesirable side effects. Thus another approach or pathway which would block or down regulate the signaling of the VEGF ligand–receptor complex was found. This was the dopamine (Dp)/dopamine receptor 2 (Dp-r2) pathway, the activation of which was involved in the regulation of angiogenic events.[23] Dopamine's binding to its receptor determines a dose-dependent inhibition of VEGFR-2 signaling.[24] Administration of high doses of dopamine agonists had been elucidated to simultaneously block tumor-related angiogenesis and VP in a mouse cancer model by interfering with VEGF/VEGFR-2 signaling.[25] Doses of dopamine agonists which were much lower than those used in the tumor model were sufficient to activate the Dp-r2 pathway and when administered at low doses simultaneously with hCG, prevented an increase in VP and did not affect angiogenesis.[24] Therefore the dopamine agonist cabergoline owing to its VEGFR-2 dephosphorylation provided a novel, specific and non-toxic approach to the prevention and treatment of OHSS, and of great clinical value in the field of ART.

Table 2 – Comparison of severe and critical OHSS.

Severe OHSS	Critical OHSS
Variably enlarged ovary	Variably enlarged ovary
Massive ascites ± hydrothorax	Tense ascites ± hydrothorax
Hematocrit >45%	Hematocrit >55%
White blood cell count >15,000	White blood cell count >250,000
Oliguria	Oliguria
Creatinine 1.0–1.5 mg/dl	Creatinine >1.6 mg/dl
Creatinine clearance ≥50 ml/min	Creatinine clearance <50 ml/min
Liver dysfunction	Renal failure
Anasarca	Thromboembolic phenomenon
	Acute respiratory syndrome

Women at risk for OHSS: candidates for cabergoline

Women at higher risk for developing OHSS are the most important candidates for institution of cabergoline and are defined by the development of 20–30 follicles larger than 12 mm in diameter during COH and retrieval of more than 20 oocytes.[6] Generally women with polycystic ovaries, those under 30 years of age, use of GnRH agonists, development of multiple follicles during treatment, high estradiol (E2) levels i.e. E2 >3000 pg/ml in serum, exposure to hCG, and previous episodes of OHSS are the most likely candidates to suffer this potentially life threatening complication and would thus benefit from drugs acting as VEGF inhibitors.[26]

Dosage of cabergoline

0.5-mg tablet of Cb2 daily for 8 days starting from the day of hCG administration is the recommended dose for prevention of this infrequent but potentially lethal complication in IVF cycles. This dose of 0.5 mg/day or a total dose 4 mg of Cb2 has been established for its prevention based on experience gained through various studies both on humans and animal models, and after consulting the literature for the average dose employed to treat prolactinomas and tailoring them.[26,27] Some published studies have even used twice the dose to be administered without any potential adverse effects.[28]

Safety profile

The safety of Cb2 use during infertility treatment, especially the ART outcome had been a concern. However it was explored and found that women at risk for OHSS who had received this drug had fertilization, implantation and pregnancy rates comparable to those of controls, matched with respect to age, number and quality of the embryos replaced, embryonic stage at transfer and sperm quality.[29] Ongoing and full-term pregnancies were also similar in each group, and no major perinatal problems were detected. Cb2 administration in early pregnancy has not revealed to be harmful either, as published studies have reported employing it up to 7 mg per week, and the frequency of spontaneous and induced abortions and major congenital malformations were comparable with rates in the general population.[30]

Efficacy of the drug

The D2 dopamine agonist cabergoline has been in use since 2002 for the prevention and treatment of OHSS showing encouraging results with a prompt hematocrit decrease, increased urine output and body weight reduction.[31] Encouraged by the various studies, many workers had tried cabergoline in OHSS prevention, administering the drug immediately after pick up or from the day of hCG administration and thus avoiding a possible detrimental effect on follicular growth and oocyte maturation due to VEGF system block, and found that none of the high risk patients treated, developed OHSS and data on pregnancy rates were comparable and implantation rates significantly higher than those observed in untreated high-responder controls.[32,33] Youssef MA et al in a latest systematic review and meta-analysis have highlighted the prophylactic action of cabergoline, in lowering the incidence of OHSS and reiterated its efficacy.[34]

Limitation in the use of cabergoline

Inspite of the proved efficacy of cabergoline as a prophylactic measure for the prevention of early OHSS its role in prevention of late onset OHSS is of limited value which has also been revealed by Carlos et al in their randomized study.[35] The other important issues pertaining to Cabergoline use concerns its VEGF targeting action. The early stages of pregnancy are highly dependent on ovarian and uterine angiogenesis as it is well known that VEGF is a key factor in endometrial neovascularisation.[33,36,37] Thus, this fundamental step in mammalian embryo implantation through VEGF-mediated angiogenesis could be intercepted by targeting VEGF with monoclonal antibodies.[38,39] However Alvarez et al in their study have presented that endometrial angiogenesis was not greatly altered, by the dose of Cb2 employed since neither implantation nor the overall ART outcome was affected.[29]

Other preventive measures

The discovery of vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine, in the pathogenesis of OHSS, and the revelation that VEGF activity could be regulated by the neurotransmitter dopamine led to various studies which finally documented the role of various dopamine agonists as a preventive measure to avert the events or symptoms associated with OHSS. After Cabergoline the next dopamine agonist to evoke interest in recent years is Bromocriptine. It has also brought about reduction in the incidence and severity of clinically significant OHSS in high risk patients without affecting the pregnancy rates.[40] Other dopamine agonists to be evaluated for their prospective role are Pergolide, Quinagolide, Talipexole hydrochloride etc. These drugs primarily used for the treatment of hyperprolactinemias and Parkinsonism when used for the treatment or prevention of OHSS needs titration of their dosages and more studies are needed to prove their efficacy in clinical practice.[41]

Low molecular weight heparin, although primarily used in the past to prevent OHSS related thrombotic complications, may also prevent OHSS occurrence independently by its antithrombotic effect, interfering with VEGF binding to its VEGF receptor 2.[42] However it is controversial and not prudently proved if prophylactic heparin should be used in the absence of abnormal coagulation.

It is hypothesized that albumin helps prevent OHSS by increasing oncotic pressure and may act as a carrier protein to sequester a vasoactive substance secreted by the corpus luteum. So administration of 20% intravenous albumin (20–40 g) at the time of oocyte retrieval is also carried out when estradiol levels are elevated, or there is a history of prior OHSS, as a preventive measure but studies of its efficacy have been mixed, and albumin treatment may risk exacerbation of ascites, allergic reactions, and virus/prion transmission. Nevertheless, a recent meta-analysis of five randomized controlled trials demonstrated that prophylactic albumin administration significantly reduced risk of developing OHSS.[43]

Metformin an insulin sensitizer added to ovulation induction in women with PCOS undergoing IVF treatment with or without cabergoline has also been documented to reduce the risk of developing OHSS. Khattab et al in their work found a significant reduction in the incidence of this complication in the group taking metformin and concluded that Metformin is a safe, cheap drug that can help in prevention of OHSS.[44]

In-vitro maturation of oocytes wherein the immature oocytes are retrieved from the antral follicles of unstimulated or minimally stimulated ovaries is a major advance in the field of ART. Though labor intensive compared to conventional IVF it offers various advantages with the most important being prevention of OHSS especially in PCOS patients who are a high-risk candidates. Apart from eliminating the risk of OHSS, it simplifies monitoring, reduces the cost of treatment, and results in fair pregnancy outcomes particularly in young age groups.[45]

Antagonist protocol vis-à-vis agonist protocol has also been documented to decrease the incidence of OHSS however the results from different centers have been conflicting. Recently, a Cochrane meta-analysis of 27 randomized clinical trials showed that antagonist use significantly reduced OHSS incidence[46]; however, this benefit was achieved at the expense of lower ongoing pregnancy and live-birth rates. The preventive effect is explained by the reduction in VEGF secretion by cumulus cells after incubation with GnRH antagonists.[47]

Thus we can say that the key to preventing OHSS is multipronged approach requiring experience with ovulation induction therapy and recognition of risk factors for OHSS. Ovulation induction regimens should be highly individualized, carefully monitored, and use the minimum dose and duration of gonadotropin therapy necessary to achieve the therapeutic goal. Preventive measures should be tailored and instituted in the high-risk cases. Along with the wide range of pharmaceutical tools in the armamentarium of a clinician for prevention, combined with in-vitro oocyte maturation and oocyte, embryo cryopreservation by vitrification and elective single embryo transfer, most of the serious complications inflicted by ART can be averted and reap the permanent benefits from this promising technology.

Conclusion

Various forms of pharmacologic tools have been used for several years by many workers for the prevention and treatment of this complication in assisted reproductive technology, without complete awareness of their mechanisms of action. The newer drugs, mainly the dopamine agonists in the light of the new pathogenetic and pharmacological evidence, should definitely be considered for prevention of OHSS. At the same time there is a clear need for large prospective randomized studies to be conducted that would compare different modalities in women at high risk of OHSS. But at the moment; prevention is the ideal treatment of OHSS.

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