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Revisiting ovarian hyper stimulation syndrome: Towards OHSS free clinic

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ABSTRACT

A rapid development and application of assisted reproductive technologies (ARTs) and ovulation-induction drugs may lead to ovarian hyper stimulation syndrome (OHSS). Young age, low body mass index (BMI), polycystic ovarian syndrome (PCOS), previous OHSS, high follicle count, and elevated serum estradiol (E2) are the certain factors that predispose women to OHSS. Many strategies have been used to reduce or avoid OHSS. Use of human chorionic gonadotropin (hCG) increases ovarian vascular permeability and is responsible for activating the vascular endothelial growth factors (VEGF) pathway and thus the entire cascade, leading to symptomatic OHSS. Gonadotropin-releasing hormone (GnRH) agonists are used as a replacement for hCG for final oocyte maturation in antagonist cycles. Reducing or eliminating the use of hCG and use of GnRH agonist triggered GnRH antagonist cycles and cryopreservation of oocytes or embryos is the most promising approach in making OHSS free clinic a reality.

KEY WORDS: Agonist, antagonist, assisted reproductive technology, GnRH, and hCG

INTRODUCTION

The presence of multiple luteinized cysts within the ovaries leads to ovarian enlargement and vascular hyper permeability causing as cites.[1] Though some degree of ovarian hyper stimulation occurs in all women who respond to ovulation induction without exogenous drugs; ovarian hyper stimulation syndrome (OHSS) as an iatrogenic complication occurs mainly due to ovarian stimulation by gonadotropins. The triggering factor for OHSS is not the ovarian stimulation or controlled ovarian stimulation (COS), but human chorionic gonadotropin (hCG) that is used to induce final oocyte maturation. Exogenous administration of hCG can lead to early OHSS and can also occur in patients who do not become pregnant. Endogenous hCG from the trophoblast can cause late OHSS in patients who become pregnant and is caused by the implanting pregnancy.[2] Clinically, OHSS can be mild or severe. While milder OHSS is relatively common and characterized by weight gain, abdominal discomfort, and enlarged ovaries; severe OHSS is accompanied by severe ascites, pleural effusion, electrolyte imbalance, and hypovolemia with oliguria. Deep venous thrombosis and embolism is the most dreaded complication of severe OHSS.[3]

There are certain factors which predispose women to OHSS, like younger age, low body mass index (BMI), polycystic ovarian syndrome (PCOS), history of OHSS, high follicle count, and elevated serum estradiol (E2) at the end of COS.[4,5] Drugs used for ovarian stimulation play a major role in the occurrence of OHSS. OHSS mostly occurs few days after hCG administration when follicular growth is medically induced by using either clomiphene citrate or gonadotropins, eventually in conjunction with agonists or antagonists of the gonadotropin-releasing hormone (GnRH).[5,6]

Many strategies have been used to reduce or avoid OHSS including use of GnRH agonists (GnRha), coasting, lowering or completely withholding hCG, elective cryopreservation of embryos, etc., Though the patients requiring hospitalization due to OHSS is < 2%,[7] but OHSS may be a serious threat to the patient's life. Further, the use

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of assisted reproductive technologies (ART) has doubled in the last decade and as per the Centers for Disease Control and Prevention (CDC), 176,247 ART cycles were performed at 456 reporting clinics in the United States during 2012.[8] This rapid expansion in use of ART, Human Fertilization and Embryology Act not allowing linking of *in vitro* fertilization (IVF) and maternal deaths, and nondisclosure by women to maternity services regarding their ART status leads us to believe that the incidence may be underestimated.[9] However, OHSS is avoidable and the concept of "OHSS free clinic" can soon be a reality. In this article, we aim to look at different aspects of OHSS and role of GnRHa in prevention of OHSS.

MATERIALS AND METHODS

A review of the literature was conducted till October 2014 for English language literature on OHSS through PubMed, Google Scholar, and the Cochrane library. Articles were selected if the target population consisted of women undergoing ovarian stimulation and evaluated OHSS as an outcome.

Classification of OHSS

Rabau *et al*., in 1967 first classified OHSS on the basis of clinical and laboratory parameters.[10] In 1978, Schenker and Weinstein, classified OHSS into three main clinical categories and six grades based on clinical severity and laboratory parameters.[11] A new and still popular classification was done in 1989 by Golan *et al*., wherein OHSS was classified into three categories (mild, moderate, and severe) and five grades (Grade 1–5).[12] In 1992, severe form was further categorized in to two subgroups by Navot *et al*.[4] In Golans classification of OHSS, categorization is done on the basis of severity and symptoms as mild (ovary size 5–10 cm), moderate (ovary size >10 cm), and severe (ovary size >12 cm) OHSS. The grading is done based on the symptoms as abdominal tension and discomfort (Grade 1), coupled with nausea, vomiting, and/or diarrhea (Grade 2). Moderate OHSS has single grade (Grade 3); where ultrasound reveals as cites and/or pleural effusion and dyspnea. Severe OHSS has two grades: Grade 4 (clinical evidence of as cites and/or pleural effusion and dyspnea) and Grade 5 (also has hemoconcentration increased blood viscosity, hypovolemia, decreased renal perfusion, and oliguria). However, as all the women undergoing IVF have enlarged ovaries and varying levels of fluid in the cavity; it is clinically difficult to classify them in grades. There is a need for a clinically relevant classification, according to the new paradigm.

Pathophysiology of OHSS

Though OHSS has been researched for quite long time, its pathogenesis still remains ambiguous. OHSS occurs due to multiple cyst formation in the ovaries after ovulation induction. The massive extravasation of fluids and proteins into the extracellular compartment under hCG stimulation leads to effusion and edema, and compensatory depletion of intravascular volume leading to hemoconcentration and thromboembolic phenomena.[11] This in turn causes reduces renal perfusion, decreases central venous pressure, and hypotension. The accompanying vasodilation leads to an increased cardiac output.[13-15] The pathology of OHSS seems multifactorial with a number of factors that are thought to trigger the cascade of events leading to OHSS. Numerous factors like estrogens, prostaglandins, rennin angiotensinogen system (RAS), interleukins, and vascular endothelial growth factors (VEGF) have been implicated as causative agents of OHSS.[16-21]

Human chorionic gonadotropin and OHSS

Exogenous hCG: hCG is the gold standard to induce final follicular maturation in IVF. For decades, hCG is being used as a surrogate for the natural midcycle luteinizing hormone (LH) surge. Both hCG and LH are endogenous ligands for luteinizing hormone receptor (LHR) which promotes follicular maturation, luteinization, and ovulation.[22] The hCG molecule has a high biological activity, which is about six to seven times higher than the endogenous LH that is replaced. Both LH and hCG bind to and activate the same receptors, but the half-life of LH is 60 min and that of hCG exceeds 24 h. hCG is thought to have a greater affinity to LHR as compared to LH, and thus exerts a more prolonged luteotropic action.[23]

The pharmacological use of hCG is reported to increase ovarian vascular permeability. It is responsible for activating the VEGF pathway and thus the entire cascade, leading to symptomatic OHSS. Cases of spontaneous OHSS have been known to occur and are reviewed in literature.[24,25] hCG has FSH-like effect that causes some ovarian stimulation. In a study in rat model for ovarian stimulation, hCG-ant dramatically reduced vascular permeability and VEGF expression that leads to OHSS.[26] The role of genetics and genetic mechanisms in OHSS is also being reviewed based on this. O'Brien and group in a study of 172 patients undergoing IVF sequenced LH/chorionic gonadotropin (LHCGR) gene encompassing the insLQ polymorphism. They found that rs4073366 C variant carrier status was associated with OHSS risk.[27]

Endogenous hCG

Along with the exogenous hCG that is administered in cases of ovarian stimulation, the role of endogenous hCG is also being researched. Two forms of OHSS have been defined, early onset, within 9 days of hCG administration; and late onset, caused due to hCG secretion by trophoblastic tissue.[28] OHSS due to endogenous hCG is usually of the

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late onset variety, where follicular enlargement occurs later through stimulation of FSHR by the hCG secreted by the trophoblast. Mutations in the FSHR, especially activating mutations that 'switch on' the receptor and make it sensitive to stimulation can be a causative agent for OHSS. FSHR gene polymorphisms, especially at codon 307 and 680 may influence FSHR protein responsiveness to exogenous FSH, and also lead to superovulation, thereby causing OHSS.[29,30] Daelemans *et al*., however, suggested that the genotype in position 680 of the FSHR cannot predict the development of OHSS, but could be a predictor of severity of symptoms among OHSS patients.[31]

GnRHa/antagonist: Reducing/eliminating hCG

GnRHa are most commonly used for IVF cycles worldwide. GnRHa leads to pituitary desensitization with subsequent gonadotropin suppression leading to a reduction in bioactive levels of LH in the serum.[32] GnRHa are also used as a replacement for hCG, for final oocyte maturation in antagonist cycles. Antagonist occupies GnRH receptors without causing downregulation. The agonist displaces the antagonist from its receptor, activating the receptor, which causes a flare up effect, inducing gonadotropin release. This agonist induced LH surge stimulates ovulation and oocyte maturation. The shorter duration of the endogenous LH surge induced by GnRHa triggering as compared with the continuous LH/hCG receptor stimulation for an estimate of 7–9 days with hCG, along with a negative impact produced by the supraphysiologic steroid levels on LH secretion by the pituitary are the most likely causes behind the reduced risk of OHSS when agonist trigger is used. In a meta-analysis of 17 randomized controlled trials by Youssef and associates, the authors concluded the risk of mild, moderate, or severe OHSS with the use of a GnRHain an antagonist-assisted reproductive technology was between 0 and 2% as compared with a 5% risk with the use of hCG.[33]

In a recent study comparing agonist triggers vs hCG in antagonist cycle, the incidence of mild-to-moderate OHSS was 16.2% with GnRHa trigger and 31.0% with hCG trigger. There was no case of severe OHSS in women with GnRHa trigger. Further, GnRHa resulted in 11.4% higher (statistically nonsignificant) live birth and ongoing pregnancy rate (odds ratio (OR) 1.73, confidence interval (CI) 0.64–4.69), with a similar difference for double-embryo transfers (OR 1.62, CI 0.44–6.38) and less need for freezing all embryos (9.7 versus 27.6%; $P = 0.04$).[34] In studies that have compared donors receiving agonist triggers vs hCG, there have been no differences in the number of oocytes retrieved, or the fertilization or implantation rates of the recipients. No OHSS was seen in these donors in any of these studies.

Use of GnRHa plays an important role in both primary and secondary prevention of OHSS. Primary prevention includes rigorous screening of patients who are undergoing IVF stimulation to identify factors that puts a patient at high risk of OHSS. These include young patients, those with PCOS, those with a high AFC, and those having a history of OHSS in a previous cycle. The antagonist protocol, because of its shorter duration and the fact that it does not cause complete pituitary suppression, is considered a safer alternative than its precursor, the long protocol, in terms of preventing OHSS. Thus, the at-risk group can be identified and started on this protocol. Softer stimulation protocols can be employed and regular E2monitoring can be followed.

Inducing final oocyte maturation with GnRHa has led to a significant reduction in the moderate and severe form of OHSS. In a randomized clinical trial of 257 oocyte donors comparing hCG to GnRHa in GnRH antagonist cycle, the fertilization rates were similar in both the groups; no case of OHSS was seen in GnRHa group, but nine cases of mild and one case of severe OHSS occurred in hCG group.[35] A recent study among 40 women with PCOS and 74 hyperresponders without PCOS also supported the routine use GnRHa trigger to prevent OHSS in women with PCOS.[36]

A meta-analysis published in 2006, as well as a Cochrane review in 2011 confirmed that OHSS can be completely avoided using an agonist trigger.[37,38]

However, in patients who underwent embryo transfer after agonist trigger, the clinical pregnancy rates were significantly lower and the miscarriage rates were higher. This was investigated and found to be due to an inadequately developed corpora lutea, insufficient stimulation of the ensuing corpora lutea, or inadequate luteal support with E2 and progesterone or a combination of all these factors.[39-41] The Cochrane review also confirmed this. They also concluded that this can be easily managed by a low dose hCG and adequate progesterone support.[37,38]

A modified luteal support regime that is practiced involves the use of E2 valerate and micronized progesterone, along with a lower dose of recombinant hCG.[42,43] However, due to the use of hCG, a small risk of OHSS remains.

With the advent of vitrification, the small risk of administering low-dose hCG as luteal support can also be eliminated completely.[44] A "freeze-all" approach in high stimulation cycles allows the ovaries to return to normal before an embryo transfer is carried out, preventing any chances of late onset OHSS caused by endogenous hCG.[45,46] GnRHa are shown to cause abolition of the spontaneous luteinization process that occurs after the LH peak; thus, the negative feedback preventing further follicular growth is lost leading to hyperstimulation. Thus, the use of GnRH antagonists ("antagonist protocol") is an alternative to

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GnRH agonists used in long protocol, especially in terms of OHSS prevention.

Dr. Paul Devroey has described a segmentation concept in management of OHSS, leading to an OHSS free clinic. It consists of optimization of the ovarian stimulation, including GnRHa triggering in a GnRH antagonist cycle (segment A). Segment B then consists of optimum cryopreservation methods for oocyte or embryo vitrification. Segment C includes embryo replacement in a receptive, nonstimulated endometrium in a natural cycle or with artificial endometrial preparation.[47] However, combining GnRHa trigger with freezing all embryos in GnRH antagonist cycles has led to anecdotal cases of severe OHSS.[48]

CONCLUSION

Prevention of OHSS becomes even more important with a rapid increase in the number of ART cycles over the years. Though predicting the occurrence of OHSS, especially late OHSS is difficult; strategies can be implied to minimize its incidence. Feasible protocols using GnRH antagonists and agonists and cryopreservation of embryos might be considered. However, it is essential for clinicians to understand that in spite of the so-called fail safe approaches provided by vitrification and subsequent transfer; there is always a small chance of OHSS. Gurbuz *et al*., reported three cases of severe OHSS after GnRHa triggering and segmentation of the cycles, without any endogenous presence or exogenous administration of hCG.[49] We also reported two cases in 2014 where severe OHSS requiring hospitalization was seen and both underwent vitrification of all embryos with a subsequent transfer. Future studies designed targeting freeze all approach and segmentation of the cycle or a fresh embryo transfer with a modified luteal phase support after GnRHa triggering would further help to clarify their role.

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