

## OHSS Free Clinic

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### Abstract

If ovarian stimulation is performed accordingly to new strategies available, the occurrence of ovarian hyperstimulation syndrome will be eradicated. The strategy is to stimulate all women with GnRH antagonist and in case of need to induce final egg maturation with GnRH agonist.

*Key words:* Ovarian stimulation, ovarian hyperstimulation syndrome, GnRH antagonist, GnRH agonist.

### Introduction

Ovarian hyperstimulation syndrome is a major iatrogenic complication of ovarian stimulation, performed for assisted reproductive technology. Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening condition with massive ovarian enlargement, ascites, hydrothorax, liver dysfunction, and renal failure. OHSS can lead in 2% to hospitalization (Papanikolaou *et al.*, 2006).

OHSS is classified in three different categories such as mild, moderate and severe. Mild ovarian hyperstimulation syndrome demonstrates weight gain, abdominal discomfort with enlargement of the ovaries. This can be measured at ultrasound and a 5-10 cm enlargement can be found on the ovaries. It can be associated with small amounts of fluid in the pelvis.

Moderate OHSS refers to more pronounced symptoms such as nausea and abdominal distension with pain, with on ultrasound large ovaries of more than 10 cm in diameter. In severe cases there is evidence for excessive third-space fluid accumulation.

As demonstrated in Table 1 the Golan classification of OHSS has been published in 1989.

For sure, there is a gradual increase in the occurrence of OHSS together with an increase in the number of IVF cycles performed worldwide. This indicates that OHSS is of a major concern. The

triggering factor of OHSS is human chorionic gonadotropin (hCG). hCG is used to trigger final egg maturation. If pregnancy occurs hCG is produced endogenously and also the cause of ovarian hyperstimulation syndrome. The trigger of the severe forms of OHSS is always the exogenous administration of hCG. The mechanism of hCG and OHSS is thought to be mediated via the significantly longer half-life of hCG as compared to LH. This mechanism leads finally to the production of the angiogenic molecule vascular endothelial growth factor (VEGF).

For sure, patients suffering from polycystic ovarian syndrome (PCOS) are the risk group for the occurrence of OHSS.

As mentioned earlier is the injection of hCG the trigger for ovarian hyperstimulation syndrome. This occurs especially in cycles where GnRH agonist has been given for down regulation.

### Are there strategies to prevent ovarian hyperstimulation syndrome?

Nowadays, we have in our hands the ideal condition of preventing the occurrence of hyperstimulation syndrome. In cycles where GnRH agonist for down regulation is replaced by GnRH antagonist, OHSS can be totally avoided by injecting GnRH agonist to trigger final egg maturation. This observation has

**Table 1.** — Golan classification of OHSS (1989).

Classification	Size ovaries	Grade	Symptoms
MILD	5-10 cm	Grade 1	Abdominal tension and discomfort
		Grade 2	Grade 1 signs plus nausea, vomiting and/or diarrhoea
MODERATE	> 10 cm	Grade 3	Grade 2 signs plus ultrasound evidence of ascites and/or pleural effusion and dyspnoea
SEVERE	> 12 cm	Grade 4	Grade 3 signs plus clinical evidence of ascites and/or pleural effusion and dyspnoea
		Grade 5	Grade 4 signs plus haemoconcentration increased blood viscosity, hypovolaemia, decreased renal perfusion, oliguria

been materialized in donor egg cycles. It has been clearly demonstrated that the association of GnRH antagonist with GnRH agonist triggering results in a total absence of ovarian hyperstimulation syndrome (Melo *et al.*, 2009).

In regular IVF cycles where GnRH antagonist is used to down regulate, it has to be considered that if patients are at risk for the occurrence of ovarian hyperstimulation syndrome for instance if more than 20 follicles are present, triggering can be performed by GnRH agonist. At this stage there are two different approaches. The first approach is to freeze all zygotes or embryos (Griesinger *et al.*, 2007; Griesinger, 2010) or GnRH agonist can be used to trigger. An adequate luteal phase supplementation has to be introduced.

With a GnRH agonist triggering an attenuated and short midcycle gonadotrophin surge has been demonstrated. By triggering with GnRH agonist special attention has to be paid to substitute the luteal phase. A classical luteal phase supplementation with progesterone and even 17 $\beta$  estradiol will not be capable to produce a sufficient number of implantations. This has been clearly demonstrated by two separate and independent studies (Humaidan, 2006; Kolibianakis *et al.*, 2005). There is one publication demonstrating in PCOS patients that progesterone IM and estradiol patches could result in acceptable pregnancy rates (Engman *et al.*, 2008).

Different approaches of supplementation in the luteal phase have been demonstrated. In administering the GnRH agonist trigger (triptorelin 0.2 mg) 1500 units of hCG has been administered at the moment of egg retrieval. By using this luteal phase supplementation protocol the luteal phase has been corrected and acceptable pregnancies have been obtained without the occurrence of OHSS (Humaidan *et al.*, 2006). In a randomized controlled trial comparing hCG triggering versus GnRH agonist triggering with low dose hCG administration

(1500 units) at the moment of egg retrieval pregnancy rates were not significantly different (Humaidan, 2009; Humaidan *et al.*, 2010).

## Conclusion

With the association of GnRH antagonist and GnRH agonist triggering the occurrence of ovarian hyperstimulation syndrome can be almost totally eradicated. The strategy to follow is to perform all first cycles in IVF with the combination of GnRH antagonist and agonist triggering. In case of pending risk agonist triggering can be performed and two options are available either to freeze all or to administer low dose hCG in the luteal phase. In this strategy ovarian hyperstimulation syndrome will be absent in our daily practice.

We have to change totally the concept of IVF to obtain an OHSS Free Clinic which is segmentation of IVF treatment in three different steps:

1. ovarian stimulation with agonist triggering avoiding OHSS
2. vitrification of all oocytes and/or embryos
3. single embryo transfer after thawing in a receptive endometrium

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