

# Ovarian hyperstimulation syndrome free IVF clinics. Myth or reality?

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## Editorial

Ovarian Hyperstimulation Syndrome (OHSS) is a condition occurring in 1–10% of in vitro fertilization (IVF) patients. Today OHSS is considered one of the most serious and even life-threatening complication of IVF. The incidence of severe morbidity after ovarian stimulation using IVF is 10–20 times higher when it is accompanied by OHSS.<sup>1</sup> The clinical manifestation of OHSS may involve, according to its severity and the occurrence of pregnancy, electrolytic imbalance, neurohormonal and haemodynamic changes, pulmonary manifestations, liver dysfunction, hypoglobulinaemia, thromboembolic phenomena, ascites and adnexal torsion.<sup>2</sup> The occurrence of approximately 3 maternal deaths per 100,000 women stimulated with VIF has been reported.<sup>3–5</sup> However, it is believed that in reality the incidences of maternal deaths due to OHSS may be underestimated.<sup>6</sup> Indeed, published data indicates a significant increase in OHSS globally and one can only agree with the Devroey et al., that “extrapolation of these figures to a global situation would give an impressive number”.<sup>3</sup>

In order to be more effective in applying preventive strategies, it is important to define the targeting group which is more sensitive to OHSS. Polycystic ovary syndrome (PCOS) is considered as a major risk factor for OHSS. Thus, while IVF cycles in general population the reported incidence of moderate to severe OHSS is 3%–8%, these numbers are increases to 10%–20% in a high-risk population of PCOS.<sup>7</sup> Recent research indicates that among PCOS patients there is a certain subgroup of women who are at higher risk of OHSS. There are certain factors which predispose women to OHSS, like younger age, low body mass index (BMI), history of OHSS, high follicle count, and elevated serum estradiol (E2) at the end of ovarian stimulation.<sup>8</sup> Among them, patients with high levels of Anti-Mullerian Hormone (AMH) and Antral Follicular Count (AFS) are specifically considered to have a higher risk for severe OHSS.<sup>9–10</sup>

Several concepts have been developed and suggestions have been made in order to prevent this complication. Among them is the “freeze all” concept of elective Frozen Embryo Transfer (FET), use of gonadotropin releasing hormone antagonist (GnRH-ant) protocol, GnRH agonist (GnRHa) triggering, use of low doses of gonadotropins and co-administration of Letrozole to ovarian stimulation protocol, are the most commonly accepted.<sup>11–15</sup> In patients with early onset

of OHSS, reinitiation of GnRH-ant in the luteal phase was shown to lead to rapid regression of the syndrome.<sup>1</sup> Similarly, a dopamine agonist or metformin administration has been recently shown as a strategy to reduce the incidence of OHSS.<sup>7,16</sup> All these protocols taken separately demonstrated excellent cumulative live birth rates and showed usefulness in lowering the frequency and severity of OHSS. However, the current the level of severe cases of OHSS still remains dangerously high ranging from 0.2% to 1% of cases.

So what is the next step? More aggressive clinical research need to be done in order to establish new therapeutic strategies for high risk OHSS patients. Based on data one can hypothesis that an ovarian stimulation protocol that combines different already proven approaches (such as the use of metformin, GnRH-antagonists, low dose gonadotropins with Letrozole co-treatment, agonist trigger and “freeze all” with FET, dopamine antagonists and/or GnRH-ant in luteal phase) might be more beneficial than each of them taken separately. The target population should be slim young women with PCOS and specifically high levels of AMH and AFS undergoing first time IVF. The clinical outcome, benefits, cost effectiveness and safety of such “combined” protocol is yet to be demonstrated in a large-scale randomized controlled trial.

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