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DEBATE

OHSS-safe IVF practice: Dream or reality?

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Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening iatrogenic complication of ovarian stimulation. Severe forms complicate 1–3% of IVF cycles (1). It is characterized by a massive ovarian enlargement together with a fluid shift into extravascular compartments responsible for the development of ascites, sometimes pleural and/or pericardial effusion, hypovolemia, oliguria, and hydroelectrolytic disorders.

Several factors such as histamine, serotonin, prostaglandins, prolactin, cytokines including the interleukins, tumor necrosis factor alpha, endothelin-1 and vascular endothelial growth factor (VEGF) are thought to be involved in triggering of increased vascular permeability after ovulation stimulation. Vascular endothelial growth factor (VEGF), which promotes angiogenesis and vascular permeability, is probably the principle factor involved in the pathogenesis of OHSS (2). VEGF was demonstrated to be secreted from progesterone-producing granulosa cells in the ovarian follicles, and the VEGF production is stimulated by HCG (3). So, it is evident that hCG is the main trigger for its development. Therefore, the ideal method to avoid OHSS occurrence is cancelation of the cycle, which unfortunately leads to a financial and psychological impact.

How to reach an OHSS-safe IVF? In the last decades, there were several trials aiming at a more successful and OHSS-safe IVF. Since the pathophysiology of OHSS is poorly understood, scientific effort should search for a reliable predictive test for patients prone to OHSS before starting stimulation and testing its validity. Such as, a possible gene mutation in the FSH receptor gene, which displays an increased sensitivity to hCG and may be responsible for the development of spontaneous ovarian hyperstimulation syndrome (OHSS), (4). Another possible option is the pre-treatment measurement of Soluble LHCGR (sLHCGR), (5). Moreover, careful controlled ovarian hyperstimulation of high-risk patients i.e., young, lean, PCO, PCOS and those with blood group A.

Triggering the ovulation using GnRH agonists instead of hCG, first introduced by Itskovitz (6) has proven efficacy in cases of ovarian stimulation when the ovary is not down regulated by GnRH agonists. Itskovitz-Eldor et al. (7) had a clinical trial in egg donors using gonadotropin-releasing hormone (GnRH) antagonist protocol and then GnRH agonist to trigger a mid-cycle LH surge. This protocol is efficient in triggering ovulation and may prevent OHSS in high responders. Another approach for patients on long protocol, who are at high risk of developing OHSS, withdrawing the agonist and replacing it with an antagonist, and triggering ovulation with an agonist bolus, could be considered without jeopardizing the safety of the patient while retaining the opportunity for success of the cycle (8).

Nikolettos et al. (9) have a trial in five cases at risk for OHSS by the continuation of 0.1 mg triptorelin for one week after embryo transfer proving its safety and effectiveness. Kol and Muchtar (10) suggested an OHSS-free protocol using rec. gonadotrophins for stimulation and added GnRH antagonist when the follicular diameter reached 13–14 mm. together with a daily dose of 75 IU of rec. LH.

The "mild" ovarian stimulation approach: a lower-than-average dose of exogenous gonadotrophins is given and gonadotropin starting from day 2 to 7 of the cycle proved its effectiveness (11). However, a few prospective randomized trials comparing "mild" vs. conventional stimulation exist, and they do not show significant results.

A new algorithm for OHSS prevention suggested the combined use of GnRH antagonist protocol with GnRH agonist triggering and adopting either a single blastocyst transfer or embryo/oocyte freezing for having a completely OHSS-free hyperstimulation (12).

Knowing that PCO is an ideal risk for developing OHSS, there are PCO cases that show good and sometimes aggressive response to the low dose of gonadotrophins. On the other hand other cases of PCO show a narrow margin between low response and aggressive response with minimal increase in the dose. Thus OHSS-safe IVF seems to be a difficult target when stimulating PCO cases. Since PCO seems to be a complex syndrome, OHSS may be considered a complex syndrome as well, that is why management of OHSS may need a multiple approach.

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