OVARIAN HYPERSTIMULATION SYNDROME: STRATEGIES FOR PREVENTION

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Ovarian hyperstimulation syndrome (OHSS) is a debilitating and potentially life threatening complication of ovulation induction. The development of OHSS is dependent upon the exposure of multiple ovarian follicles to human chorionic gonadotropins after ovulation induction with gonadotropins. Presumably, along with triggering ovulation and subsequent luteinization, hCG elicits a follicular inflammatory reaction associated with the release of vascular permeability factors - primarily VEGF- which results in increased vascular permeability and transudation of protein rich fluid from the intravascular to the extra-vascular space. Thus, OHSS is a vascular leak syndrome which can be associated with ovarian enlargement, abdominal distention, hemoconcentration, electrolyte imbalance, liver and kidney dysfunction, and rarely thromboembolic complications.

Prevention of OHSS relies on identifying patients at risk and individualization of ovarian stimulation protocols. Patients at particularly high risk for OHSS include young women with high antral follicle counts and high anti-mullerian hormone (AMH) levels, and women with polycystic ovarian disease,. Prevention relies on decreasing the pool of developing follicles (reducing granulosa cell mass) by administering the lowest effective gonadotropin doses and careful dosage titration. In the face of extreme ovarian responses, cycle cancellation avoiding hCG administration may be necessary.

Withholding gonadotropins ("Coasting") in individuals who exhibit extremely high estradiol levels (>3000 pg/ml) and delaying hCG administration until E2 levels drop to 2,000- 2,500 pg/ml appears to reduce but not totally eliminate the incidence of OHSS. Presumably depriving the smaller follicles of FSH induces atresia and reduces the granulose cell pool. Cryopreservation of all embryos and avoiding transfer in the cycle of stimulation appears to reduce the incidence of OHSS by eliminating the risk of exposure to rising hCG concentrations during early pregnancy. In general, IVF stimulation protocols with GnRH antagonists are associated with a lower incidence of OHSS. Moreover, with the latter protocols, a GnRH agonist can be used as the ovulatory trigger to elicit an endogenous LH surge in women who exhibit excessive ovarian responses - as this avoids the prolonged ovarian exposure to hCG with its longer half-life. Similarly, recombinant LH can be used for the same purpose, albeit this is impractical as high dose preparations are likely to be very expensive. Other prevention approaches include decreasing the ovulatory hCG trigger dose and the use of cabergoline. Cabergoline, a dopamine receptor agonist, is believed to reduce vascular permeability by inhibiting phosphorylation of VEGF-2 receptors. This last method has been only partially successful as it appears to diminish the incidence of moderate but not of pregnancy associated severe OHSS. Although some investigators have advocated the prophylactic use of albumin and hydroxyl-ethyl starch for women at risk for OHSS it is important to emphasize that these methods do not eliminate the syndrome and that the most effective approach for reducing OHSS is the identification of patients at risk and individualization of stimulation protocols.