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Treatment with exogenous gonadotrophic hormones has been used for more than 40 years. It has been more than two decades since they have been the "golden standard" in assisted reproductive techniques. The key issue of using gonadotropins was the improvement of pregnancy rates through retrieval of multiple mature oocytes and increasing the number of replaced embryos (1). However, one of the challenging complications is ovarian hyperstimulation syndrome (OHSS), a dramatic and potentially life-threatening complication. Though the reported incidence of the severe form of OHSS is small (0.5 to 5%), it is an iatrogenic complication of a non-vital treatment (2). Despite a great deal of basic science and clinical research, its pathophysiology is still poorly understood. Since OHSS lacks a specific treatment, prevention has been in focus. Many risk factors have been identified and various methods for preventing OHSS or diminishing its severity have been suggested to avoid withholding hCG and cycle cancellation. Though most of the investigators suggest the use of coasting to prevent OHSS, well-designed studies to confirm its preference to other strategies and to standardize application criteria are still lacking (3). Unfortunately, because of inability to consistently identify patients at risk, there is no consensus about its prevention strategies, mostly dealing rather late with the problem when OHSS seems impending, and hence achieve only partial

Debate Prevention of OHSS

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success.

Like many other diseases, OHSS is the result of what is inherited and what is added. The role of the former may prevail completely (4) or partially (5). The added factor, the stimulation protocol, should gain more attention. Ideally, ovulation induction should stimulate the ovaries only to a desired level of ovulation. No doubt the overutilization of high-dose gonadotrophin protocols by assisted reproductive units today carries some responsibility for the occurrence of OHSS. In fact, refinements in drug regimens are needed not only to address OHSS, but also other undesired consequences, such as multiple pregnancies and increased costs. In this respect, there is need to reconsider the use of biochemical markers to identify patients at risk before ovarian stimulation. Predicting ovarian response to ovarian stimulation appears to have substantial benefit in counseling and in tailoring each stimulation protocol according to the expected ovarian response.

In recent years much new information related to regulation of human follicle development has become available (6). Most of the studies concerning biochemical markers of ovarian responsiveness (basal FSH, LH, E2, and inhibin-B) have been directed towards identification of poor responders. In reproductive endocrinology, the use of ratios of interacting markers (7, 8), rather than absolute values (9), seems to be more informative. The basal FSH concentration is negatively correlated with the ovarian stimulation response, reflecting the balance between ovarian steroids and peptides and the hypothalamic-pituitary axis during follicular recruitment but before selection of the dominant follicle. The less FSH stimulation required to allow development of the follicular cohort, the better the quality of the developing follicles, as gauged by response to gonadotropin stimulation (10). It seems reasonable to assume that better quality is likely to be reflected by increased E2 production with a subsequently higher basal E2 level. Hence, the E2/FSH ratio would be more useful as a predictor of ovarian response in normally ovulating women (8). It is already known that high basal E2 (above 290 pmol/L) mostly reflects diminished ovarian reserve as a result of already advanced follicular development with fewer follicles in the developing cohort that may still be rescued with exogenous gonadotropin therapy (8, 11). Suppressed by way of a negative feedback mechanism, cycle day 3 FSH levels appear to have diminished prognostic accuracy in such a case, as the elevated basal E2 and low FSH values result in a misleadingly high E2/FSH ratio. On the other hand, with lower basal E2 (at or below 290 pmol/L), the F2/FSH ratio was found to be closely related to ovarian reserve. The correlation of the E2/FSH ratio with parameters of ovarian response to HMG stimulation was better, in terms of spectrum and precision, than either basal F2 or FSH alone. In these cases, the basal E2 value reflects ovarian response to the stimulating effect of basal FSH that is not yet suppressed by negative feedback. Compared to others (12), E2/FSH ratio represent an "endogenous dynamic" test for evaluation of ovarian reserve. E2/FSH ratio of 35 or higher in these cases was found to be associated with a relative risk of 12.7 for ovarian follicular overresponse (8), and hence seems to be promising in predicting OHSS. Reviewing the data of Seifer et al. (13) showed a better response to stimulation in association with high basal inhibin-B and low basal FSH, inferring higher inhibin-B/FSH ratios. In fact, the combined use of the gonadal steroid (E2)/FSH ratio and gonadal peptide (inhibin-B)/FSH ratio is likely to reflect more closely the degree of readiness of the follicular cohort and eventually enhance our present ability to predict outcome before starting ovarian stimulation. The additional use of biophysical markers seems to be of great value (14-16). These parameters are currently under investigation in a larger patient sample to enhance prediction of ovarian responsiveness before therapy begins.

The use of hMG in ART aims at multifollicular development and the step-down hMG protocol seems rational as it mimics the physiological events during the natural ovarian cycle (6). Earlier, the aim was to define general rules for appropriate hMG dosage (17), though individualization, according to the characteristics of the patient, should be also considered. The starting "recruiting" dose is adjusted according to the predicted ovarian responsiveness, with
stepping-down to a "trophic" maintenance dose when ultrasonographic monitoring (usually by stimulation day 7) reveals the advancement of a reasonable number of antral follicles to 10-mm in diameter or more. However, many studies confirm that the duration (related to the window concept) rather than the magnitude (threshold concept) of FSH stimulation determines the number of developing follicles (6). The impact of this concept, in management of patients with risk factors, is that earlier close monitoring - serum E2 (18) and ultrasound (revealing discrepancy in endometrial and follicular development) - could be of value in disclosing early evolution of OHSS. This would allow earlier stepping-down of hMG dose. The rescued follicles, with their enhanced sensitivity for FSH as they mature, continue their development despite relatively low FSH concentrations, incapable of stimulating growth of less mature follicles. Adopting this "early step-down" approach might abolish OHSS through curtailing of the number of functionally active "down" approach might abolish OHSS through curtailing of the number of functionally active small and medium-sized follicles, along with slowing down of escalation in E2 level, both known as major risk factors (3). This approach might be viewed as a further development of conventional (19) and early (20) "coasting", yet avoiding the risk of abrupt E2 fall with a reduction of the oocyte retrieval rate and embryo quality. In conclusion, it seems that multiple strategies needs to be adopted to avoid OHSS, yet much attention should be paid to those operating earlier during ART therapy.

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Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic life-threatening complication of ovarian stimulation in Assisted Reproductive Techniques. In spite of the extensive researches and articles published upon the preventive measures for the syndrome, there is a feeling that we are still faraway from an effective and completely safe preventive strategy for the syndrome, which at the same time will not jeopardize the oocytes and embryos quality as well as the pregnancy rate. In the literature the authors gave an outstanding different opinions on the same preventive option. In the following we try to summarize the value of each preventive option and the different opinions on each option.

Defining patients at risk and adjusting the stimulation protocol

The first important step of prevention is the identification of risk factors, in order to individualize the patient's stimulation regimen. PCOS patients are the most vulnerable group for the development of the syndrome. While it is believed that both E2 and ultrasound monitoring is necessary, it is insufficient as most IVF centers still report the occurrence of severe forms of OHSS, even though such monitoring is practiced (1). A serum E2 level of 12,315 pmol/ L (3,354 pg/ ml) on day 11 of ovarian stimulation gives a sensitivity and specificity of 85% for the detection of women at risk for OHSS (2). Strict monitoring does however allow the application of a number of preventive measures when ovarian response is exaggerated.

Canceling the cycle

Canceling the cycle and withholding HCG is the only method which totally avoids the risk of OHSS in ovarian induction cycle or in IVF. All other procedures usually succeed in decreasing either the risk or the severity of OHSS rather than totally preventing it (3). When GnRH agonists or antagonists are not used, one should remain vigilant, since a spontaneous LH peak may still occur, resulting in a pregnancy that is sometimes associated with OHSS complications (4).

Intravenous albumin

The suggestion that i.v. albumin might prevent the development of severe OHSS was first made in 1993 (5). In the literature, the dose of i.v. albumin varies between 20-50 g and the time of its administration was either; before, during or immediately after oocyte retrieval. This dose was not adjusted according to the serum albumin level. A Cochrane Review on the use of i.v. albumin to prevent severe OHSS, included five randomized controlled trials that enrolled 378 women (193 in the albumin - treated group and 185 in the control group). A meta-analysis of the five included trials showed a significant reduction in severe OHSS by administration of human albumin, but it did not lead to complete prevention. No second dose was given later on except in one study (6). Kamel in 2003 adjusted the dose according to the drop of serum albumin level (7).

Other volume expanders such as hydroxyethyl starch

As an alternative to human albumin, 1000 ml 6% hydroxyethyl starch solution may be infused at the time of oocyte collection, followed by another 500 ml 48 h later (8). Although there was no significant reduction in the severe OHSS cases, but there was a high significant decrease in moderate OHSS in the i.v. starch group. In a prospective randomized, double -blind, placebo - controlled