

## Avoidance of Ovarian Hyperstimulation Syndrome through Early Prediction and Manipulation of Stimulation

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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<sup>1</sup>

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<sup>2</sup>. 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<sup>3</sup>. 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 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<sup>4</sup> or partially<sup>5</sup>. 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 over-utilization 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<sup>6</sup>. Most of the studies concerning biochemical markers of ovarian responsiveness (basal FSH, LH, E<sub>2</sub>, and inhibin-B) have been directed towards identification of poor responders. In reproductive endocrinology, the use of ratios of interacting markers<sup>7, 8</sup>, rather than absolute values<sup>9</sup>, 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<sup>10</sup>. It seems reasonable to assume that better quality is likely to be reflected by increased E<sub>2</sub> production with a subsequently higher basal E<sub>2</sub> level. Hence, the E<sub>2</sub>/FSH ratio would be more useful as a predictor of ovarian response in normally ovulating women<sup>8</sup>. It is already known that high basal E<sub>2</sub> (above 80 pg/ml) 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<sup>8, 11</sup>. 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 E<sub>2</sub> and low FSH values result in a misleadingly high E<sub>2</sub>/FSH ratio. On the other hand, with lower basal E<sub>2</sub> (at or below 80 pg/ml), the F<sub>2</sub>/FSH ratio was found to be closely related to ovarian reserve. The correlation of the E<sub>2</sub>/FSH ratio with parameters of ovarian response to HMG stimulation was better, in terms of spectrum and precision, than either basal F<sub>2</sub> or FSH alone. In these cases, the basal E<sub>2</sub> value reflects ovarian response to the stimulating effect of basal FSH that is not yet suppressed by

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negative feedback. Compared to others<sup>12</sup>, E<sub>2</sub>/FSH ratio represent an "endogenous dynamic" test for evaluation of ovarian reserve. E<sub>2</sub>/FSH ratio of 35 or higher in these cases was found to be associated with a relative risk of 12.7 for ovarian follicular over response<sup>8</sup>, and hence seems to be promising in predicting OHSS. Reviewing the data of Seifer et al<sup>13</sup>. 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 (E<sub>2</sub>) /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<sup>14-16</sup>. These parameters, along with basal antimüllerian hormone (AMH)<sup>17</sup> 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<sup>6</sup>. Earlier, the aim was to define general rules for appropriate hMG dosage<sup>18</sup>, 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<sup>6</sup>. The impact of this concept, in management of patients with risk factors, is that earlier close monitoring -serum E<sub>2</sub><sup>19</sup> 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 small and medium-sized follicles, along with

slowing down of escalation in E<sub>2</sub> level, both known as major risk factors<sup>3</sup>. This approach might be viewed as a further development of conventional<sup>20</sup> and early<sup>21</sup> "coasting", yet avoiding the risk of abrupt E<sub>2</sub> 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.

## References

1. Abd-el-Maeboud K., Khalifa E., El-Hussein E. An Increased Number of Replaced Embryos Counteracts the Adverse Effect of Hydrosalpinges on IVF/ET Outcome. *J Assist Reprod Genet* 1998; **15(1)**: 22-6.
2. Delvigne A., Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Hum Reprod Update* 2002; **8(6)**:559-77.
3. Aboulghar M., Mansour R. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. *Hum Reprod Update* 2003; **9(3)**:275-89.
4. Montanelli L., Delbaere A., Di Carlo C., et al. Mutation in the follicle-stimulating hormone receptor as a cause of familial spontaneous ovarian hyperstimulation syndrome. *J Clin Endocrinol Metab* 2004; **89(3)**:1255-8.
5. McElhinney B., Ardill J., Caldwell C., et al. Ovarian hyperstimulation syndrome and assisted reproductive technologies: why some and not others? *Hum Reprod* 2002; **17(6)**:1548-53.
6. Fauser B., Van Heusden A. Manipulation of Human Ovarian Function: Physiological Concepts and Clinical Consequences. *Endocrine Reviews* 1997; **18(1)**:71-106.
7. Abd-El-Maeboud K., Eissa S., Kamel AS. Altered endometrial progesterone/oestrogen receptor ratio in luteal phase defect. *Dis Markers* 1997; **13**:107-16.
8. Abd-El-Maeboud K. Basal estradiol/follicle-stimulating hormone ratio predicts ovarian response to gonadotropic stimulation in patients with normal ovulation. *Advances In Therapy* 1999; **16(4)**:164-74.
9. Kligman I., Rosenwaks Z. Differentiating clinical profiles: predicting good responders, poor responders, and hyperresponders. *Fertil Steril* 2001; **76(6)**:1185-90.
10. Scott R., Hofmann G., Oehninger S., et al. Intercycle variability of day 3 follicle-stimulating hormone levels and its effect on stimulation quality in in vitro fertilization. *Fertil Steril* 1990; **54(2)**:297-302.
11. Smotrich D., Widra F., Gindoff P., et al. Prognostic value of day 3 estradiol on in vitro fertilization outcome. *Fertil Steril* 1995; **64(6)**:1136-40.
12. Fanchin R., de Ziegler D., Olivennes F., et al. Exogenous follicle stimulating hormone reserve test (EFFORT): a simple and reliable screening test for detecting "poor responders" in in-vitro fertilization. *Hum Reprod* 1994; **9(9)**:1607-11.
13. Seifer D., Lambert-Messerlian G., Hogan J., et al. Day 3 serum inhibinB is predictive of assisted reproductive technologies outcome. *Fertil Steril* 1997; **67(1)**:110-4.

14. Frattarelli J, Lauria-Costab D., Miller B., et al. Basal antral follicle number and mean ovarian diameter predict cycle cancellation and ovarian responsiveness in assisted reproductive technology cycles. *Fertil Steril* 2000; **74**(3):512-7.
15. Ng EHY, Tang OS, Ho PC. The significance of the number of antral follicles prior to stimulation in predicting ovarian responses in an IVF programme. *Human Reprod* 2000; **15**(9):1937-42.
16. Yong P., Baird D., Thong K., et al. Prospective analysis of the relationships between the ovarian follicle cohort and basal FSH concentration, the inhibin response to exogenous FSH and ovarian follicle number at different stages of the normal menstrual cycle and after pituitary down-regulation. *Human Reproduction* 2003, **18**(1):35-44.
17. van Rooij I., Broekmans F., Velde E., et al. Themmen APN. Serum anti-Müllerian hormone levels: a novel measure of ovarian reserve. *Hum Reprod* 2002; **17**(12):3065-71.
18. van Hooff MHA. The human menopausal gonadotropin (HMG) dose in in vitro fertilization (IVF): what is the optimal dose? *J Assist Reprod Genet* 1995; **12**(4):233-5.
19. Schoot D., Hop W., de Jong F., et al. Initial estradiol response predicts outcome of exogenous gonadotropins using a step-down dose regimen for induction of ovulation in polycystic ovary syndrome. *Fertil Steril* 1995; **64**(6):1081-7.
20. Levinsohn-Tavor O., Friedler S., Schachter M., Raziel A, Strassburger D, Ron-El R. Coasting-what is the best formula? *Hum Reprod* 2003; **18**(5):937-40.
21. Egbase P., Al-Sharhan M., Grudzinskas J. 'Early coasting' in patients with polycystic ovarian syndrome is consistent with good clinical outcome. *Hum Reprod* 2002; **17**(5):1212-6.