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Suggestions on the use of LH

To the Editor:

Dr. Filicori's editorial on the role of LH in infertility treatment (1) was thoughtful and provocative. He, pointed out that during the normal menstrual cycle, LH progressively increases during the few days before the LH surge, during the critical final stages of oocyte maturation. However, not only do the levels of immunoreactive LH increase, but the concomitant increase in estrogen causes the pituitary to secrete LH that is more bioactive (2). This marked increases in bioactive LH is likely related to the optimal health of the oocyte, and it is becoming increasingly clear that improved IVF outcome can be aided by providing LH activity with certain GnRH agonist and antagonist regimens.

We reported data (3) indicating that leuprolide, at full dose, is associated with levels of bioactive LH/hCG before hCG injection that are significantly lower than early follicular phase levels in spite of injection of three vials of hMG which contains an average of 10 U of hCG per vial in addition to the 75 U per vial of LH. The frequent use of pretreatment with the oral contraceptive pill causes LH levels to be even lower.

The innovative use of low-dose hCG during gonadotropin treatment may restore physiologic aspects to treatment regimens, but perhaps some caution is warranted to ensure that levels are not excessive in magnitude or duration. We have compared levels of bioactive LH during leuprolide with levels in controls receiving only hMG. Despite giving hCG at about a mean diameter of 14 mm in the controls 2 days earlier than with agonist, we observed more than a two-fold increase in bioactive LH compared with day 3 levels. It is possible that prolonged levels of high bioactive LH played some part in the lower pregnancy outcome before introduction of agonists and in the observation of lower implantation rates with less than optimal doses of GnRH antagonist (4). Low-dose hCG is a logical method to provide LH-like activity. We have shown that in normal women with a 14-mm follicle given a GnRH antagonist, 50 U of hCG restored the levels of bioactive-LH/hCG to normal (5). Dr. Filicori subsequently showed that this dose was sufficient to induce the development of oocytes with excellent implantation potential in a woman with hypogonadotropic hypogonadism; we have had similar success using this dose in that clinical setting. Since 50 U was not excessive at 14 mm, before the preovulatory increase in bioactive LH, it is possible that brief use of 200 IU, as suggested, may induce regression of small follicles without an adverse impact on mature follicles.

The prospect that such a simple and inexpensive approach could be used to reduce the risk of ovarian hyperstimulation syndrome and multiple pregnancies in hyperresponding patients is exciting, and Dr. Filicori should be congratulated on his innovative look at controlled ovarian hyperstimulation.

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February 8, 2003

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Reply of the Author:

I wish to thank Dr. Meldrum for the kind comments contained in his letter related to my editorial published in the February issue of Fertility and Sterility (1). I feel that no further specific response is needed to his letter.

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February 19, 2003

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Does it all come down to postnatal aging of the primary oocyte?

To the Editor:

I read with interest the article by Chuang et al. (1). We have reached similar conclusions that when evaluating out-

come of IVF-ET, advanced age is a better prognosticator of poor outcome than elevated early follicular phase serum FSH (2). Our study similarly concluded that elevated FSH in younger patients is more associated with decreased number of oocytes retrieved (2).

It is attractive to attribute the poorer prognosis with increased FSH with advanced age to different etiologies for the diminished oocyte reserve; that is, that natural selection of recruitment of the best follicles leaves behind not only fewer but the worst oocytes with physiologic aging versus some damaging process in younger women that leaves diminished reserve but similar quality of oocytes to peers with normal FSH (1).

However, there is another hypothesis that could explain this phenomenon. Data suggest that controlled ovarian hyperstimulation (COH) can create an adverse uterine environment inhibiting implantation (3). In addition, studies indicate that the older uterus is more susceptible to the adverse effects of COH based on higher or similar implantation rates in older patients (but not younger patients) with deselected frozen–thawed embryos compared to fresh ET (4).

One way to support the authors' hypothesis would be to evaluate the effect of age and FSH in the absence of COH. Such a study of patients not undergoing IVF-ET has been published (5). The results showed a 6-month clinical and ongoing pregnancy rate of 46.1% and 34.6%, respectively, in women younger than 40 years of age 10.5% and 5.3% in those 40 years of age or older despite similar (about 20 mIU/mL) serum FSH levels ($P < .05$) (5). These data from this latter study thus eliminates the possibility that the COH effect on the uterus rather than lesser-quality oocytes could account for the demonstrated age related decreased pregnancy rate in women with increased FSH. Thus, this study supports the authors' hypothesis (5).

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February 10, 2003

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Reply of the Authors:

We thank Dr. Check for valuable comments regarding our study (1). In a series of studies, Dr. Check et al. (2) first showed that advanced age is a better prognosticator of poor outcome of IVF-ET than elevated early follicular phase serum FSH level. They further demonstrated that age-related decrease in fertility is due primarily to fewer quality oocytes rather than to controlled ovarian hyperstimulation (COH) effects on endometrial receptivity in IVF cycles (3).

One recent study from United Kingdom addressing the issue of biological aging of the oocyte (as indicated by basal serum FSH levels) versus chronological aging has reached similar conclusions that ovarian aging affecting oocyte quality and fecundity can occur independent of chronological age (4). Furthermore, the U.S. national experience on clinical outcome among recipient of donor eggs (5) has shown that the success of donor egg therapy is unaffected by recipient age up to the later forties, after which they begin to decline. These results support the possibility that age-related uterine factors play a role in the decline in fertility with increasing age.

To summarize, the findings have important practical implications whereby serum basal FSH measurement may be a valuable prognostic index, through chronological age.

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February 17, 2003

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