Letters to the Editor

Effects of LH on oocyte yield and developmental competence

Dear Sir,

Tesarak and Mendoza (2002) found that LH activity supplementation in oocyte donors enhanced FSH-induced folliculogenesis and increased the number of retrieved oocytes; conversely, exogenous LH administration appeared to negatively affect embryo morphology and implantation rates in subjects who had serum LH levels \( \geq 1 \) IU/l after steroid and GnRH agonist suppression. However, this interesting article failed to address a number of critical methodological and conceptual issues.

In this study hMG was used to supplement LH. Nevertheless, hCG also significantly contributes to the LH activity content of the hMG preparation used by the authors (Filicori et al., 2001), and hCG is detectable in peripheral serum after the administration of 75 IU/day of hMG (Filicori et al., 2002a); thus, just measuring LH on day 8 is inadequate to characterize the LH activity milieu during hMG treatment and serum hCG determinations should have been added. The authors also fail to indicate when, and by whom, the presence of embryonic sacs was checked and if ultrasound was carried out always at the same week of gestation; heterogeneity in the execution and timing of this procedure could have affected outcome in an uncontrolled manner. Furthermore, problems exist regarding the study design and statistical analysis of the results. The authors state in the introduction that this was a prospective, randomized study but then fail to specify which of the many parameters they assessed were their primary outcome variables and the pre-study calculations to determine sample size, as mandated by the CONSORT guidelines (Moher et al., 2001). It is well known that the chance of a spurious positive finding increases with the number of questions posed, if no actions are taken to protect against the inflation of false positive findings from multiple statistical tests (Committee for Proprietary Medicinal Products, 2002). The 5% level was used as cut-off for claiming statistical significance and no adjustments for numerous comparisons were carried out; thus, the identification of significant differences might have occurred purely by chance and the results of the statistical analysis of this study should be interpreted carefully.

Even if we concede that LH activity administration negatively affected treatment in the study’s group 4, there are at least two possible explanations for these findings. First, differences may have existed in the subjects treated with the various regimens of this protocol or among the recipients. Unfortunately, the authors failed to characterize properly the study’s participants, as age was the only parameter reported. Were baseline hormone levels measured (e.g. gonadotrophins, androgens, insulin)? Were they normal and/or not significantly different among subgroups of donors and recipients? Were the study participants properly screened for reproductive disorders such as endometriosis? How frequent was the occurrence of the polycystic ovary syndrome (PCOS) and insulin resistance in the study population? PCOS, which is known to be associated with a significantly increased rate of pregnancy wastage after after assisted reproduction treatment (ART) (Ludwig et al., 1999), is commonly detected in young women in the age range of this study; it is highly unlikely that subjects with this disorder were not treated if 253 unselected young oocyte donors were included in the study. Insulin resistance is associated with increased miscarriage rates (Jakubowicz et al., 2002); was this parameter assessed in oocyte recipients? Because of the set-up of the study it is possible that a bias in patient selection was introduced and/or that a subgroup of subjects prone to developing early gestation disorders and/or particularly sensitive to LH administration was chosen. In this case the results of the study could be unrelated to LH or dependent upon a patient-related problem; then, the conclusions of the study would be unwarranted or not applicable to all the conditions when LH activity is supplemented for ovulation induction, as implied in the abstract.

The second possible explanation for the study’s outcome is that, as suggested by the authors, a ‘window’ for optimal LH action exists; thus, higher levels of LH activity (contributed by a combination of endogenous and exogenous sources) would have negatively affected embryo quality and implantation rates (i.e. a dose-dependent detrimental action of LH activity). This interpretation, however, goes against the conclusions of several recently published studies that the authors failed to reference. Ng et al. (2001) found no difference in implantation rates in patients treated with recombinant FSH or hMG, while a favourable implantation rate was associated with LH activity administration in the studies of Schoolcraft et al. (1999) and Gordon et al. (2001). In the work of the authors themselves (Mendoza et al., 1999; 2002) higher follicular fluid levels of LH were found to be strongly associated with a positive outcome of assisted reproduction; LH was higher in follicles producing oocytes that gave rise to ‘embryos with best morphology and fastest cleavage rates’ and pregnancy; inexplicably, the authors failed to cite and discuss their own work in this area.

Finally, it is understandable how LH activity administration could have enhanced the number of mature follicles and oocytes, and reduced FSH dose requirements, as previously reported (The European Recombinant Human LH Study Group, 1998; Filicori et al., 2002b); this stimulatory action on folliculogenesis was the likely result of exogenous LH activity interaction with granulosa cell receptors that develop in intermediate size follicles after a few days of FSH administration (Zeleznik et al., 1984). Conversely, the authors failed to propose a convincing pathophysiological mechanism to explain the detrimental effects that the addition of a mere

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75 IU/day of hMG appeared to cause on embryo quality and implantation rates in patients with higher endogenous LH levels. Despite hMG administration, serum LH concentrations in the authors’ study remained well below the levels present in the normal follicular phase of spontaneous menstrual cycles, and hCG is barely detectable in serum after 75 IU/day of hMG (Filicori et al., 2002a). Much larger amounts of LH activity are commonly administered to patients undergoing controlled ovarian stimulation when hMG only is employed, and less intense pituitary suppression regimens are often applied (Strehler et al., 2001); despite this, no untoward effects of LH activity have been detected. We recently tested mid-late follicular phase administration of far larger amounts of LH activity to drive folliculogenesis: exploring uncharted territories in physiological process, in search for recovery of multiple follicles whose granulosa cells are devoid of LH receptors (Campbell et al., 1999). If LH activity harmed oocytes and embryos in a dose-dependent manner this treatment should have triggered a catastrophic outcome we did not observe in this report and in several other patients who received similar gonadotrophin regimens (data not published).

References


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