IS LH NEEDED FOR ROUTINE OVARIAN STIMULATION REGIMENS USING FSH?
S. Daya
Hamilton, Ontario, Canada

The evolution in the development of gonadotropins for clinical use has witnessed a progressive change from the reliance on preparations derived from human urine to the now routinely available preparations derived in-vitro using recombinant technology. The use of cell lines to ensure the production of a protein molecule that is stable and consistent is central to the process of producing recombinant gonadotropins and obviates the concerns about inconsistencies associated with the extraction of gonadotropins from human urine. The experience with using recombinant gonadotropin is that it is a generally favourable but more costly option. These cost considerations have led to the purification of urinary gonadotropin preparations so that a lower cost alternative can be offered to patients undergoing treatment. This approach requires the demonstration that treatment efficacy is not compromised and has led to an ongoing debate on which preparation is better from both economic and effectiveness considerations. Although the original urinary-derived gonadotropins were administered as a combination of FSH and LH, further purification permitted the use of FSH-only preparations. Today, the use of recombinant technology has made available both FSH and LH for clinical use and has generated a debate on whether LH is needed in ovarian stimulation regimens. This debate has witnessed a renewed call for the use of purified urinary human menopausal gonadotropin (hMG), which contains both LH and FSH, for ovarian stimulation. Attempts to resolve this debate will require a review of the role of LH in folliculogenesis and a comparison of the highly purified urinary gonadotropin and recombinant gonadotropin preparations from an efficacy perspective.

The role of LH in folliculogenesis: The two-cell, two-gonadotropin model is a fundamental concept in ovarian physiology that establishes a role for both LH and FSH in hormone production. Androgen production and release during folliculogenesis is dependent on the stimulation of the theca cells by LH. The theca cells are in close contact with the granulosa cells that proliferate during follicular growth and which are stimulated by FSH to induce the expression of the aromatase enzyme. Thus, androgens produced by the theca cells are then transferred to the granulose cells where they can be converted to estradiol by aromatase action. Hence, both gonadotropins are involved in estradiol production during folliculogenesis.

The finding of LH receptors in granulosa cells during the intermediate follicular phase (1-3) suggests that LH has a supplementary role at this time. Growth factors, such as insulin growth factors I and II, are expressed by both granulosa and theca cells during folliculogenesis and are important in promoting follicular maturation. It is believed that LH plays a role in inducing and maintaining this paracrine system by its action on both granulosa and theca cells. Thus, once granulosa cells express sufficient receptors for LH, the activity of FSH can be replaced by administering LH alone (4). It is not clear when in the follicular phase this action of LH on granulosa cells begins, but the local production of factors is necessary for granulosa cell growth and regulation of oocyte maturation.

During follicular growth, the selection of the dominant follicle occurs despite declining FSH levels because the selected follicle expresses FSH receptors with a lower threshold (i.e., higher receptivity) than the non-selected follicles. It has been suggested that LH has a third role by assisting in deselected these non-dominant follicles. The rapid increase in LH levels at mid-cycle (LH surge) causes a suspension of further granulosa cell mitosis and permits final oocyte maturation to begin and luteinization of the cumulus-oophorus to occur. The high levels of LH prevent further growth of the non-dominant follicles. This concept has led to the proposal of the ‘LH ceiling’ hypothesis wherein each follicle has an upper limit of responsiveness to LH beyond which follicle maturation ceases and degeneration occurs (3). Thus, the dominant follicle would have a much higher ceiling than the non-dominant ones, leading to their regression at the time of the LH surge.

Effect of high levels of LH on reproductive outcome: Adverse outcomes from elevated serum LH levels have been observed in a variety of studies. A significant reduction in the rate of fertilization was observed in women with raised basal LH levels (greater than one standard deviation from the mean) undergoing treatment with IVF with ovarian stimulation using clomiphene citrate (CC), hMG or a combination of the two (5). In another study, in women undergoing IVF treatment with a combination of CC and hMG there were no pregnancies recorded if the urinary output of LH was elevated when measured two days prior to the day of hCG administration (6). In women with polycystic ovary syndrome, the effect on outcome of the high endogenous levels of LH was observed in a study using pulsatile GnRH to induce
ovulation; basal LH levels were lower in women who conceived compared to those who did not, and the rate of miscarriage was higher in those who had elevated levels of LH compared to those who had ongoing pregnancies (7).

The effect of raised LH levels in the follicular phase of spontaneous menstrual cycles was also investigated and found to be detrimental. A higher likelihood of pregnancy was observed when the LH level was <10 IU/L and the miscarriage rate was significantly higher in women with LH levels >10 IU/L (8).

The effect of reduced LH levels on reproductive outcome: The introduction of the GnRH agonist into the ovarian stimulation regimen resulted in a significant improvement in outcome with IVF treatment because cycle cancellation resulting from a premature surge in LH levels was reduced significantly and pregnancy rates were increased. However, GnRH agonist administration results in levels of LH during the phase of follicular development that are lower than in spontaneous cycles raising concerns that the levels of LH may be insufficient to support folliculogenesis particularly when recombinant FSH alone is used for ovarian stimulation. Measurement of serum LH levels on day 7 of stimulation in normogonadotropic women permitted the evaluation of different threshold levels on reproductive outcome using receiver operator characteristic curves (9). It was evident that regardless of the cut-off level selected (i.e., 0.5, 0.7 or 1.0 IU/L), no adverse effect was observed on pregnancy and miscarriage rates. Similarly, in another study on day 8 of stimulation levels of LH, 1.5 IU/L were not associated with any detrimental effect on clinical pregnancy rates (10). However, when the cut-off level was >1.5 IU/L, reduction in fertilization and clinical pregnancy rates was observed.

Collectively, these observations indicate that although GnRH agonist is very effective in preventing an LH surge, the resulting low levels LH are sufficient to permit folliculogenesis despite the fact that no exogenous LH is administered. Consequently, the role of supplementing the ovarian stimulation regimen with a preparation containing LH is questionable.

Efficacy of adjunctive administration of LH: The value of adding LH to the ovarian stimulation regimen requires evaluation with randomized controlled trials. Two strategies have been employed with this objective in mind; comparison of FSH with HMG, and comparison of FSH with FSH plus LH. A meta-analysis was conducted pooling the results of four trials comparing recombinant FSH with HMG in normogonadotropic women undergoing treatment with assisted reproduction with a GnRH agonist long protocol (11). Although outcome data on ongoing pregnancy and live birth were not available for all trials to perform separate meta-analyses on these outcomes, and despite the presence of clinical heterogeneity, the authors chose to pool the results anyway using the outcome that was available. No statistically significant differences were observed in the rates of ongoing pregnancy/live birth per woman. Secondary outcomes (such as total dose of gonadotropins used, number of oocytes retrieved, and rates of cancellation, multiple pregnancy, miscarriage, ovarian hyperstimulation syndrome) were all similar in the two treatment groups.

Several randomized trials have been conducted comparing FSH with FSH plus recombinant LH. In one small trial in normogonadotropic women undergoing treatment with assisted reproduction using the GnRH agonist long protocol, the outcomes of administering highly purified FSH at a daily dose of 150-450 IU were compared with those in the experimental group receiving the same dose of FSH but with supplementation with recombinant LH at a daily dose of 75 IU from stimulation day 1 (12). No significant differences were observed between the two groups in any of the outcome variables measured.

In a larger trial in women undergoing treatment with ICSI with GnRH agonist in the long protocol, the outcomes of administering recombinant FSH at a daily dose of 225 IU were compared with those in the experimental group receiving the same dose of FSH but with supplementation with recombinant LH at a daily dose of 150 IU from stimulation day 6 (13). Despite transferring higher numbers of embryos in the group receiving LH, no significant differences in pregnancy rates were observed between the two treatment groups.

A third trial was conducted in normogonadotropic women undergoing treatment with assisted reproduction with GnRH agonist in the long protocol (14). The control group received recombinant FSH at a daily dose of 150-300 IU, whereas the experimental group received additional administration of recombinant LH in a 1:2 ratio with FSH from stimulation day 8. No significant differences were observed between the two groups in cycle performance indicators or pregnancy rates.
Collectively these observations emphasize that the addition of LH (either in the form of HMG or as recombinant LH) to the stimulation regimen with FSH (using either highly purified urinary or recombinant preparations) in women undergoing treatment with assisted reproduction using the GnRH agonist long protocol (which is the most commonly used regimen) provides no additional benefit in terms of improved clinical outcome. The cost implications of such additional therapy further support the lack of value of supplementary LH therapy.

Conclusions: The evidence from studies evaluating folliculogenesis clearly support the role of LH in terms of facilitating the production of estradiol, supporting intraovarian production of growth factors, and in preventing the further growth of secondary follicles as the dominant follicle reaches maturity and ovulation. Amount of circulating LH in excess of the ‘ceiling threshold’ are likely to be associated with adverse reproductive outcomes. Despite the reduction in circulating levels of LH with the use of GnRH agonists in protocols used in assisted reproduction, the amount of LH that is still available is sufficient to permit adequate follicular development and achievement of pregnancy without the need for supplementation with exogenous LH. Thus, in routine use for assisted reproduction in normogonadotropic women, recombinant FSH alone is sufficient for ovarian stimulation rendering the use of supplementary administration of LH unnecessary.

References
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