Luteinizing hormone and its dilemma in ovulation induction

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ABSTRACT

Concept of a 'therapeutic window' of luteinizing hormone (LH) for successful conception in assisted reproductive technology and ovulation induction has been reviewed in this literature. The separate but complementary roles of follicle stimulating hormone and LH in stimulating folliculogenesis and ovulation are well established. Levels under which low LH concentrations may be equally or suboptimally needed for oocyte quality and subsequent embryonic development competence has been reviewed along with the data related to the high levels of LH promoting follicular atresia.

KEY WORDS: Effects on ovulation, LH ceiling, ovulation induction

INTRODUCTION

Luteinizing hormone (LH): A hormone released by the pituitary gland in response to luteinizing hormone- releasing hormone. It controls the length and sequence of the female menstrual cycle, including ovulation, preparation of the uterus for implantation of a fertilized egg, and ovarian production of both estrogen and progesterone. Theca cells in the ovary respond to LH stimulation by secretion of testosterone, which is converted into estrogen by adjacent granulosa cells. In women, ovulation of mature follicles on the ovary is induced by a large burst of LH secretion - the preovulatory LH surge. Residual cells within ovulated follicles proliferate to form corpora lutea, which secrete the steroid hormones - progesterone and estradiol. Progesterone is necessary for the maintenance of pregnancy, and, in most mammals, LH is required for continued development and function of corpora lutea.

PRINCIPLES OF OVULATION INDUCTION AND THE ROLE OF LH IN FOLLICULOGENESIS

Before we proceed to explore the effects and the potential therapeutic applications of LH on ovulation induction, it is extremely important to first gain a clear understanding of not just the normal physiology of LH and ovulation but also certain basic principles involved in ovulation induction. The follicular phase features a series of sequential actions of hormones and autocrine–paracrine peptides on the follicle, leading the follicle destined to ovulate through a period of initial growth from a primordial follicle through the stages of pre-antral, antral and preovulatory follicle. The two-cell, two-gonadotrophin model is a fundamental concept in ovarian physiology that establishes a role for both LH and follicle stimulating hormone (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 granulosa cells where they can be converted to estradiol by aromatase action. Hence, both gonadotrophins are involved in estradiol production during folliculogenesis. The finding of LH receptors in granulosa cells during the intermediate follicular phase 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.[1] 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 deselecting 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.[2] 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. It has been shown that low-dose stimulation with low-dose LH enhances steroidogenesis without inhibiting cell proliferation whereas high dose LH suppresses granulosa proliferation, initiates atresia of immature follicles and premature luteinization of preovulatory follicles. Another important concept is that of the FSH threshold and window. Administration of gonadotrophins at levels below a threshold does not elicit any ovarian response even when prolonged therapy is used. The FSH threshold is exceeded in the normal cycle during the late luteal and early follicular phase as a result of reduced steroid production from the regressing corpus luteum. The duration of FSH elevation above the threshold levels is limited by a decrease in FSH concentrations around the mid-follicular phase due to the negative feedback exerted by increasing estradiol and inhibin production from growing follicles. This FSH window is important in the determination of the number of developing follicles. If this window is extended in ovulation induction cycles, the recruited cohort of follicles is enlarged and more follicles will eventually develop to the preovulatory stage.

A great deal of discussion has been dedicated to the gonadotrophin need of the developing follicles. As described in the classic "two-cells–two-gonadotrophin" theory, LH is needed to provide the granulosa cells with androgen precursors for estradiol biosynthesis. FSH alone can induce follicle growth, but without LH, estradiol levels remain low and pregnancy will not occur. There is no debate about the need for both hormones in women with hypogonadotropic hypogonadism, but there is significant disagreement about the need for LH in "endocrinologically normal" women. This review analyses whether or not all patients need LH for follicular growth stimulation and new opportunities for improved treatment as a result of the availability of recombinant human LH both in patients with ovulatory disorders (World Health Organization (WHO) groups I and II anovulatory patients) and those undergoing multiple follicular development for assisted reproduction.

IS LH NEEDED IN THE LATE FOLLICULAR PHASE?

The real or presumed benefits of various gonadotrophin preparations were brought up by a number of researchers. A study done on 50 young normal responders analysed results obtained with recombinant FSH (rFSH) and human menopausal gonadotrophin (HMG) during *in-vitro* fertilization (IVF).[3] They underwent intracytoplasmic sperm injection (ICSI) treatment for male factor infertility and were given either HMG or rFSH after luteal phase downregulation with depot gonadotrophin releasing hormone agonist (GnRHa). The researchers found that in the HMG group, the length of stimulation was shorter and fewer ampoules of gonadotrophin were needed to get the cycle to the retrieval stage. Serum LH and estradiol levels were also higher. On the other hand, with rFSH stimulation, more follicles were seen during stimulation, more oocytes were retrieved, more mature oocytes were obtained, and more embryos were available for transfer. There was no difference in the implantation and pregnancy rates, however. The same study[3] also discussed the results of midcycle LH measurements in GnRHa-downregulated IVF cycles that resulted in conception and those that did not. They did not find a significant difference between LH levels measured in conception and non-conception cycles. Further, they did not find a difference in LH levels between cycles that resulted in ongoing pregnancies and pregnancy loss.

Another study[4] also evaluated the role of recombinant LH (rLH) during IVF cycles. They randomly assigned women who were undergoing IVF treatment, following luteal phase GnRHa downregulation and stimulation with rFSH, to either receive additional placebo or rLH once the largest follicles reached 14 mm in diameter. Although peak estradiol levels were higher in the rLH group, the number of eggs, mature eggs, number and quality of embryos, and pregnancy rates were similar between the two groups. However, these investigators did not measure midcycle LH levels. Rather than supplementing everybody with LH or measuring LH levels, they recommended that the decision

to supplement be based on estradiol levels and endometrial thickness. When estradiol levels are low and there is poor endometrial development, they would recommend supplementation with exogenous LH. Similar to the outcome for the luteal phase GnRHa-downregulated cycles, there was not much benefit in adding LH to stimulation in cycles for which the GnRH antagonist is used.

To review the discussion about LH supplementation during IVF, a study[5] analysed the combined results of two studies that their group had performed, which showed significantly higher clinical pregnancy and delivery rates (49% vs 36%) among women who received HMG following luteal GnRHa downregulation, when cycle day 1 LH level was below 1.2 IU/L. The level 1.2 IU/L was used as the cut-off because this is the mean endogenous LH level in women with hypogonadotropic hypogonadism who were shown to benefit from LH supplementation. He attributed the group's findings to lower fertilization rate, poorer embryo quality, and increased rate of spontaneous abortion when LH levels were low.

Although FSH is essential to stimulate ovarian folliculogenesis, increasing physiological and clinical evidence suggests that moderate LH stimulation may also be critical for optimal follicle and oocyte development.

To assess the endocrine and clinical effects of LH activity supplementation administered in the mid-follicular phase during controlled ovarian hyperstimulation to poor responders who were candidates for *in vitro* fertilization (IVF) embryo transfer, a prospective, controlled, non-randomized trial with historical controls was done.[6] Twenty-five IVF patients who had shown a poor response to standard, long-protocol GnRHa and FSH only in a preceding cycle (cycle A), were stimulated in the next cycle after six months with hCG supplementation (50 I.U. subcutaneously daily) starting on day 7 during standard, long-protocol GnRHa and FSH (cycle B). The comparative analysis of clinical effects (duration of stimulation, total highly purified (HP)-FSH dose, number of oocytes retrieved and pregnancy rate) and endocrine responses (serum E2, follicular E2 and androstenedione levels) were determined between cycles A and B. Maximum serum E2 levels and clinical pregnancy rate were higher in cycle B, with hCG supplementation. Also, the follicular E2 and androstenedione levels were higher in cycle B. No differences were noted between cycles as regards to the duration of stimulation, total HP-FSH dose and number of oocytes retrieved and the study concluded that the LH activity supplementation in the mid-follicular phase yields favorable pregnancy results in low responders. This may be due to enhanced release of follicular precursors for greater synthesis of E2.

Another study showed how LH plays critical roles in the control of folliculogenesis and ovarian function in humans.[7] LH activity administration during gonadotrophin ovulation induction can enhance ovarian response and optimize treatment. More specifically, LH activity (both LH and low-dose hCG) can support the growth and stimulate the maturation of larger ovarian follicles as a result of specific granulosa cell receptors that develop after a few days of FSH priming. This action of LH is independent of FSH, and it has been shown recently that the last stages of follicular development can be supported by sole administration of LH activity in the form of low-dose hCG, without causing premature luteinization.

Although the role that LH plays in folliculogenesis is still controversial, recent evidence points toward facilitatory actions of LH activity in ovulation induction. Thus, a study[8] compared the response to either highly purified FSH (75 IU FSH/ampoule; group A, 25 subjects) or human menopausal gonadotrophin (75 IU FSH and 75 IU LH/ampoule; group B, 25 subjects) in normoovulatory GnRH agonist-suppressed women, who were candidates for intrauterine insemination. A fixed regimen of two daily ampoules of highly purified FSH or human menopausal gonadotrophin was administered in the initial 14 days of treatment; menotropin dose adjustments were allowed thereafter. Treatment was monitored with daily blood samples for the measurement of LH, FSH, 17beta-estradiol E(2), progesterone, testosterone, hCG, inhibin A, and inhibin B, and transvaginal pelvic ultrasound was performed at two-day intervals. Although preovulatory E(2) levels were similar, both the duration of treatment (16.1±0.8 vs. 12.6±0.5 days; $P<0.005$) and the per cycle menotropin dose (33.6±2.4 vs. 23.6±1.1 ampoules; $P<0.005$) were lower in group B. The study concluded that ovulation induction with LH activity-containing menotropins is associated with shorter treatment duration, lower menotropin consumption, and reduced development of small ovarian follicles. These features can be exploited to develop regimens that optimize treatment outcome, lower costs, and reduce occurrence of complications such as multiple gestation and ovarian hyperstimulation.

A number of clinical trials have compared the efficacy of r-hFSH and urinary FSH in women undergoing assisted reproductive technology (ART). In general, these have shown that fewer FSH ampoules are required to achieve ovarian stimulation with r-hFSH, while the number of oocytes retrieved and embryos produced are higher than with urinary FSH, clinical pregnancy rate per cycle started is significantly higher, higher implantation rates were seen in patients treated with r-hFSH than in those treated with urinary FSH, suggesting that embryo viability is increased. The finding that FSH preparations produce effective

ovarian stimulation compared to human menopausal gonadotrophins in women undergoing ART raises the question of whether LH is required for ovarian stimulation. Results have suggested that implantation rates may actually be lower in women who received exogenous LH. Such studies suggest, therefore, that in normogonadotropic women, the addition of LH to an r-hFSH regimen does not add any further clinical benefit and may actually be detrimental.[9] However, the addition of LH should still be considered in individual patients on a case by case basis, particularly in candidates who are poor responders.

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.[10] 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.[11] 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.

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.[12] 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.[13] 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.[14] 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.[15]

THE PCOS PARADIGM

Polycystic ovary syndrome (PCOS), a relatively common reproductive endocrine disorder often associated with high endogenous LH secretion, menstrual cycle disorders, infertility and high rates of spontaneous abortion, was considered the paradigm condition that proved the potential untoward actions of LH. LH-stimulated theca cell androgen secretion may be involved in the promotion of atresia of non-dominant follicles in the normal menstrual cycle. Growing evidence is pointing towards defining PCOS as a mostly metabolic disorder, with limited untoward effects directly linked to high LH secretion. Excessive insulin levels appear to be causing the majority of the reproductive endocrine disruptions of PCOS. Patients with PCOS have increased LH relative to FSH, but LH is modified by body mass index (BMI). A study was conducted on 24 women to determine whether the impact of BMI on neuroendocrine dysregulation in PCOS is mediated at the hypothalamic or pituitary level.[16] The results of the study showed that BMI was negatively correlated with mean LH, LH/FSH, and LH pulse amplitude but there was no effect of BMI on LH pulse frequency. Percent inhibition of LH was decreased in PCOS, compared with normal women, suggesting an increase in the amount of endogenous GnRH, but was not influenced by BMI.

THE RELATIONSHIP BETWEEN LUTEINIZING HORMONE AND HYPERANDROGENISM?

Some studies tend to imply that LH excess worsens hyperandrogenism through ovarian stimulation of androgenesis. This is unlikely to be valid despite the fact that a major neuroendocrine component of PCOS involves alterations in LH secretion, and primary LH excess has long been considered the cause of the excess ovarian androgen secretion in PCOS. This concept simply arose because of the known stimulatory effect of LH on theca cell function and the elevation of serum LH levels at baseline and in

response to GnRH in classic PCOS. In hyperandrogenemic girls destined to develop PCOS, the nocturnal increase in ovarian steroids may not be adequate to suppress the GnRH pulse generator, leading to a persistently rapid LH pulse frequency, impaired FSH production, and inadequate follicular development.[17]

Circulating levels of LH are essential for the production of steroid hormones that regulate the timing of ovulation and target tissue responses, as well as maintenance of the corpus luteum and therefore early pregnancy. Clinical and basic science observations show that elevated levels of serum LH during the follicular phase of the menstrual cycle are not only unnecessary for follicular maturation but are deleterious to normal reproductive processes. These elevations may occur as a result of administration of exogenous LH or through an endogenous pathological process like in PCOS. Resting levels of LH, synergizing with locally produced IGFs, inhibin and perhaps other growth factors, are adequate for normal follicular growth and steroidogenesis. Elevations in serum LH above these resting levels may result in increased androgen production that diminishes follicular function and reduces early embryo viability. Elevated LH levels during the preovulatory period may also negatively influence post-ovulatory events such as conception and implantation. With these facts in mind, the best results for ovulation induction would be expected with purified FSH administration to women following GnRH downregulation. One may, therefore, envisage the role of LH during the follicular phase of the menstrual cycle to be a crescendo: of little importance during the early follicular phase and most important at the time of ovulation. FSH, on the other hand, has a reversed pattern of importance: essential for early events and having a relatively minor role at the time of ovulation.[18] Although LH receptors have not yet been identified in oocytes, excessive LH may disrupt granulosa cell communication in the cumulus–oophorus, which is critical to maintain the oocyte in the dictyate stage of meiosis until ovulation.[19,20] Thus, according to this theory, abnormal oocyte maturation could be responsible for the reduced fertility and increased miscarriage rates frequently encountered in PCOS. Growing evidence is pointing towards defining PCOS as a mostly metabolic disorder, with limited untoward effects directly linked to high LH secretion. Excessive insulin levels appear to be causing the majority of the reproductive endocrine disruptions of PCOS. Furthermore, insulin-lowering drugs improve glycodelin levels (an endogenous compound linked to embryo implantation) and significantly reduce the incidence of miscarriage in patients at risk.[21] These positive effects cannot be achieved by reductions of endogenous LH secretion, for instance with GnRH analogs. Thus, it appears that the hypersecretion of LH in PCOS is simply an epiphenomenon, possibly related to chronic anovulation and reduced progesterone secretion, relative increments of estrogens such as estrone and unbound 17b-estradiol, or a combination of these factors. Recently, it was also shown that excessive LH secretion alone is not the cause of ovarian hyperandrogenism. The lack of any cause±effect relationship between LH hypersecretion and reproductive system disorders, particularly in PCOS, clearly undermines theories of detrimental actions of LH on fertility.

The defect in steroidogenesis must be the result of escape from normal downregulation of thecal cell secretion rather than over-stimulation by LH. If we accept these results, then the fundamental defect underlying the androgen excess of PCOS is ovarian hyper-responsiveness to gonadotrophin action because of escape from downregulation and not a primary result of excess LH *per se*. Taken together, all these observations suggest that dysregulation of androgen biosynthesis is an intrinsic property of PCOS theca cells. Hence, the evidence suggests that LH is not a major player in the hyperandrogenism of PCOS, and excess LH may be a consequence of the metabolic alterations in PCOS.

From a clinical point of view it is axiomatic that LH supplementation must be used for the induction of ovulation in WHO Group I patients. Nevertheless, this may not be valid for WHO group II patients and for patients under ART for different reasons.

CONCLUSION

The separate but complementary roles of FSH and LH in stimulating folliculogenesis and ovulation are well established. However, it is not known if there are levels under which low LH concentrations may be equally or suboptimal for oocyte quality and subsequent embryonic development competence. On the other hand, there are some conflicting data related to the high levels of LH promoting follicular atresia and early miscarriage. This has lead to the concept of a 'therapeutic window' of LH for successful conception in ART and ovulation induction. As can be seen from the opposing results presented by various groups, the controversy surrounding the role of LH in ovarian stimulation has certainly not been resolved. Although FSH is universally recognized as the key driver of ovarian follicle growth and maturation, the role of LH in these processes is more controversial. Future studies are needed to better identify those who would benefit from the addition of LH.

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