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Research Article

# Recombinant LH in Ovarian Stimulation as a Personalized Medicine

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## Abstract

The number of babies born from assisted reproductive technology is increasing year by year. During this procedure some drugs are used to stimulate the ovaries. The combination of drugs and their dosing is known as a "protocol" which are designed to achieve maximum oocyte yields. Although the doses and rates are always a matter of debate.

Luteinizing hormone is essential for normal follicular development and oocyte maturation. Nevertheless, the use of this drug in an ovarian stimulation cycle has been widely discussed.

This review evaluates the effect of recombinant luteinizing hormone supplementation on ovarian stimulation and the outcomes in reproductive medicine the most recent studies.

***Keywords:*** *Assisted Reproduction Technologies; LH Supplementation; Ovarian Stimulation*

## Abbreviations

FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; HMGs: Human Menopausal Gonadotropins (HMGs, or Menotrophin); rFSH: Recombinant FSH

## Introduction

Ovarian stimulation occurs with the administration of hormone medications (ovulation drugs) that stimulate the ovaries to produce multiple eggs. Sometimes called enhanced follicular recruitment or controlled ovarian stimulation. During the last years several protocols have been used to perform an effective ovarian stimulation.

The gonadotrophin preparations first used for ovulation induction contained both FSH and LH activity. Human pituitary extracts were used first as a source of gonadotrophins, and then post-menopausal urine became an alternative source for gonadotrophin preparations. Human menopausal gonadotropins (HMGs, or menotrophin) are a combination of FSH and LH in a 1 : 1 ratio that is extracted from urine obtained from postmenopausal women. Afterwards, recombinant FSH (rFSH), devoid of LH activity, was introduced into the market around 1995, and it keeps as the commonly used by many fertility centers worldwide.

## Materials and Methods

### Folliculogenesis and ovarian stimulation by gonadotrophins

To understand the ovarian stimulation process, we must go back to the physiology and previous articles. Two gonadotrophins, FSH and LH, play major roles in the endocrine regulation of ovarian folliculogenesis. The granulosa cells are the target for FSH, which promotes their proliferation and aromatase expression. LH acts on theca cells through cell surface receptors to promote androgen production in the early follicular phase. The androgen produced in theca cells is a substrate for the FSH-stimulated granulosa cell aromatase system that catalyses the conversion of androgen into oestrogen [1]. This action of gonadotrophins is called the 'two cell–two gonadotrophin system' [2]. Oestradiol production and secretion is needed for the pre-ovulatory gonadotrophin surge and for uterine and endometrial changes required for embryo implantation. FSH also stimulates granulosa cell LH receptor expression in the late follicular phase [3,4]. Once granulosa cells express LH receptor, they also become receptive to LH stimulation, like theca cells [5], and LH can exert most of the stimulatory effects of FSH, including stimulation of the aromatase system [6]. There is an interaction between this endocrine system and paracrine factors (steroids, cytokines and other growth factors). FSH and LH together stimulate granulosa cells to produce inhibin, which is an important paracrine factor acting on theca cells for androgen synthesis.

Serum FSH and LH concentrations show an inverse secretory pattern in the follicular phase.

FSH concentrations are elevated in the early follicular phase, which stimulates follicle growth and development, then they decline in the mid to late follicular phase by increasing oestrogen secretion from maturing follicles [7]. Serum LH concentrations that are low in the early follicular phase progressively increase thereafter [8]. As oestrogen peaks, an LH surge is triggered which causes the mature oocytes to be released. During the luteal phase, serum FSH concentrations are reduced and start increasing a few days before menses.

FSH and LH play complementary roles in stimulating follicle growth and ovulation. Ovarian follicle growth and development is not solely dependent on FSH [9]. LH contributes to this process when granulosa cells of the follicles become receptive to LH, and larger follicles (10 - 12 mm) with LH receptors keep growing due to decreasing FSH concentrations in the mid to late follicular phase [10]. In addition, increasing intra-ovarian androgen with continuing stimulation of the theca cells with LH and decreasing FSH concentrations in the late follicular phase cause atresia of the small follicules [11,12].

So, luteinizing hormone plays an important role in follicle growth by contributing to follicle maturation, fertilization and embryo quality.

Till now the optimal amount of LH or FSH/LH ratio becomes an important issue.

## Results and Discussion

### Recombinant LH administration in assisted reproductive technology

Over the last two decades, several scientific attempts have been proposed to maximize controlled ovarian stimulation, the most appropriate protocol that yields the optimum number of oocytes for fertilization is still controversial. Although till now a general and astonishing protocol doesn't exist because treatments need to be adapted to individual patient's characteristics. Nowadays personalized medicine is transforming healthcare and different protocols can be implemented.

Previous studies might have failed to find any effect of using exogenous LH as a supplementation to FSH because they did not segregate population by groups.

Tailored protocols should consider women's clinical background, age, and ovarian reserve. Accordingly, rLH supplementation in different groups of assisted reproduction patients will be discussed.

### Recombinant LH administration in normogonadotrophic women undergoing assisted reproduction

This is most patients that are treated by reproductive medicine. Studies published show that no benefit is obtained by combining LH and FSH in ovarian stimulation for IVF in normogonadotropic patients when using GnRH analogues. This is especially true for an unselected population. A summary of the studies is showing in table 1.

| Study | Number of participants | Protocol in ovarian stimulation | Conclusion |
|---|---|---|---|
| Sills., *et al*. (1999) [13] | 30 | FSH protocol (150-450 UI) + 75 UI LH daily from initiation of stimulation | No significant differences |
| Balash., *et al*. (2001) [14] | 30 | FSH 450 UI+ 75 UI LH daily from initiation of stimulation | No significant differences |
| Humaidan., *et al*. (2004) [15] | 231 | F SH 150-300 UI + LH from day 8 of stimulation | Significant difference |
| Sauer., *et al*. (2004) [16] | 73 | FSH 225 UI + 150 UI LH from antagonist initiation day | No significant differences |
| Griesinger., *et al*. (2005) [17] | 127 | FSH 150 UI + 75 UI LH from day 6 | No significant differences |
| Tarlatzis., *et al*. (2006) [18] | 114 | FSH 150 UI + 75 UI LH when leading follicle reached 14 mm | No significant differences |
| Fabregues., *et al*. (2006) [19] | 129 | FSH 450 UI+ 150 UI LH (step down protocol) | No significant differences |

***Table 1:*** *Evaluation of the addition of LH in normogonadotropic women.*

### Recombinant LH administration in population (above 35-year-olds) undergoing assisted reproduction

Patients above 35 years old but mostly above 39 years old present a crucial issue, the ageing of the oocytes. This fact along with diminished ovarian reserve and ovarian responsiveness, is a contributing factor in the low success rate of assisted reproduction.

A recent study analyzed this issue in a large, age adjusted, randomized controlled trial in which rFSH vs rFSH + rLH stimulation were compared in the GnRH antagonist protocol. This study has shown that, while cycle outcome is equal in both protocols in young populations (up to 35 years old), a significantly better implantation rate with a clinically relevant better ongoing pregnancy rate per started cycle was achieved in a older population (36 - 39 year olds) receiving r-FSH + r-LH from stimulation day one.

Advanced meta-analysis shows that r-hFSH/r-hLH cotreatment and r-hFSH monotherapy have comparable clinical pregnancy rates in women above the age of 34 years. However, women between 35 and 40 year old, might benefit from r-hFSH/r-hLH co-treatment in terms of clinical pregnancy and implantation rates [20-27].

## Conclusion

In general, it can be concluded that in most patients, FSH alone is sufficient to achieve optimal results in ovarian stimulation for assisted reproduction. However, when a patient hadn't achieved a pregnancy after some attempts, is advisable to consider a supplementation with exogenous LH. The group that would benefit most from this treatment might be the specific assisted reproduction populations

like women of advanced reproductive age (≥ 35 years), patients with endometriosis or low ovarian reserve. In view of the fact that the action of LH at the follicular level may restore the follicular milieu in these patients, in whom oocyte quality and, therefore, embryo quality and implantation rates are restored.

Further studies are required in these specific population.

## Conflict of Interest

No conflicts of interest to disclose.

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