Recombinant luteinizing hormone supplementation in assisted reproductive technology: a systematic review

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Objective: To assess the role of recombinant human LH (r-hLH) supplementation in ovarian stimulation for ART in specific subgroups of patients.
Design: Systematic review.
Setting: Centers for reproductive care.
Patient(s): Six populations were investigated: 1) women with a hyporesponse to recombinant human FSH (r-hFSH) monotherapy; 2) women at an advanced reproductive age; 3) women cotreated with the use of a GnRH antagonist; 4) women with profoundly suppressed LH levels after the administration of GnRH agonists; 5) normoresponder women to prevent ovarian hyperstimulation syndrome; and 6) women with a "poor response" to ovarian stimulation, including those who met the European Society for Human Reproduction and Embryology Bologna criteria.
Intervention(s): Systematic review.
Main Outcome Measure(s): Implantation rate, number of oocytes retrieved, live birth rate, ongoing pregnancy rate, fertilization rate, and number of metaphase II oocytes.
Result(s): Recombinant hLH supplementation appears to be beneficial in two subgroups of patients: 1) women with adequate prestimulation ovarian reserve parameters and an unexpected hyporesponse to r-hFSH monotherapy; and 2) women 36–39 years of age. Indeed, there is no evidence that r-hLH is beneficial in young (<35 y) normoresponders cotreated with the use of a GnRH antagonist. The use of r-hLH supplementation in women with suppressed endogenous LH levels caused by GnRH analogues and in poor responders remains controversial, whereas the use of r-hLH supplementation to prevent the development of ovarian hyperstimulation syndrome warrants further investigation.
Conclusion(s): Recombinant hLH can be proposed for hyporesponders and women 36–39 years of age. (Fertil Steril® 2018;109:644–64. ©2018 by American Society for Reproductive Medicine.)
Key Words: Luteinizing hormone (LH), recombinant LH, ovarian stimulation, IVF/ICSI, ART

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Gonadotropin therapy is pivotal in ovarian stimulation. Its introduction in medical practice dates to almost a century ago and represented a major advance in infertility treatment (1). Whereas FSH is the main regulator of antral follicular growth, LH plays key roles in promoting steroidogenesis and in the development of the leading follicle. Moreover, LH exerts different functions during the different stages of both natural and stimulated cycles.

LH is a glycoprotein hormone synthesized by the anterior pituitary gland under the stimulation of GnRH (2). It consists of two noncovalent linked peptide subunits, α and β. The three-dimensional structure and the active conformation of the subunits are maintained by internal disulfide bonds (3). Subunit α is identical in all gonadotropins, whereas subunit β confers biologic specificity and has characteristic biologic and immunologic properties (4). Separated peptide subunits lack biologic activity. A heterodimeric protein binds to the LH receptor and causes signal transduction. Glycosylation is essential for the biologic function of LH and reflects a differential spectrum of bioactivities, and half-lives of LH isoforms (5). The composition of LH isoforms, their longevity, and their properties vary during the menstrual cycle and reproductive life. For example, isoforms with a shorter half-life but higher biopotency are more frequent in young women than in menopausal women (6). During the menstrual cycle, the ratio of biologic to immunologic activity slowly increases during the follicular phase, peaks at midcycle, and decreases during the luteal phase (5, 7). This pattern is greatly influenced by the addition of a sialic acid ("sialylation") or a sulfonic group ("sulfonation") to the terminal part of the carbohydrate moieties of the LH β subunit. Specifically, sialylation is associated with a prolonged half-life and sulfonation accelerates hormone elimination (8). This change in isoform profile seems to be essential for ovulation (9). LH binds to the LH/hCG receptor (LHCG-R), which belongs to the family of G protein–coupled receptors endowed with seven transmembrane domains and a large N-terminal extracellular domain. The intramolecular domain involves adenyl cyclase via coupling to G proteins (10). LHCG-Rs are located on ovarian theca, granulosa, and luteal cells. LHCG-R is also present in extragonadal tissue (11) and may exert extragonadal effects on implantation (12), regulation of oviduct and cervical functions (13, 14), modulation of endometrial angiogenesis and growth (15), brain development, and sexual behavior (11). However, the physiologic significance of these findings remains to be established (11).

Both FSH and LH exert crucial activity during folliculogenesis. The "two cell–two gonadotropin" model was long the mainstay of our understanding of folliculogenesis (16). According to this concept, LH stimulates theca cells thereby advancing androgen production, and FSH governs the proliferation of granulosa cells (GCs) and promotes E_2 synthesis. More recently, the two cell–two gonadotropin concept was expanded with the finding that LH receptors are also expressed on GCs, especially after follicular selection, and their expression is ~10 times higher in the GCs of preovulatory follicles than in antral follicles 3–10 mm in diameter (17). LH upregulates E_2 output and aromatase CYP19 mRNA expression (18, 19). Moreover, it cooperates with FSH in inducing local production of androgen, inhibin B, and growth factors (20). Among these, insulin growth factors 1 and 2, which are expressed in both GCs and theca cells throughout folliculogenesis, are important promoters of follicular maturation (21–23).

A large body of data on the use of exogenous LH supplementation in controlled ovarian stimulation (OS) for assisted reproductive technology (ART) has accumulated over the past 20 years. However, no clear picture emerges regarding the clinical use of recombinant human LH (r-hLH) in OS for ART. This could be related to the fact that previous meta-analyses included different types of patients in the same group, making it difficult to determine in which women LH supplementation could be recommended (24, 25). Consequently, to identify which women could benefit from r-LH supplementation, we conducted a systematic review to evaluate the efficacy of exogenous r-hLH in specific subgroups of women undergoing ART.

MATERIALS AND METHODS

Search Strategy

We performed a systematic literature search in the Medline/Pubmed and Scopus databases. The end date for these searches was May 2017. The overall strategy for study identification and data extraction was based on the following key words, alone or combined, "luteinizing hormone," "recombinant LH," "rLH" "rhLH," "ovulation induction," "assisted reproductive technology," "ART," "in vitro fertilization," "IVF," "poor responders," "hyporesponse" (Supplemental Table 1; available online at www.fertstert.org). The reference lists of relevant reviews and articles were hand searched.

Eligibility and Data Extraction

Eleven investigators with expertise in the field of reproductive medicine examined randomized control trials (RCTs) in which r-hFSH–alone protocols were compared with r-hFSH + r-hLH supplementation in the following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) populations: 1) women with a hyporesponse to exogenous r-hFSH monotherapy; 2) women at an advanced reproductive age ($\geq$35 y); 3) women cotreated with the use of GnRH antagonist; 4) women with profoundly suppressed LH levels after the administration of GnRH agonists during OS; 5) normoresponder women to prevent ovarian hyperstimulation syndrome (OHSS); and 6) women with a poor response to OS, including those who met the European Society of Human Reproduction and Embryology (ESHRE) Bologna criteria (26). Hyporesponders were defined as normogonadotropic women with a normal ovarian reserve who required elevated doses of r-hFSH (>2,500 IU) to achieve an adequate number of oocytes or who had a steady response in terms of both follicular growth and E_2 level during OS.

Data extraction was performed independently by three authors (C.A., A.C., and S.C.E.) with the use of predefined data fields.