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Clinical significance of fixed r-hFSH: r-hLH supplementation in controlled ovarian stimulation

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Abstract

Luteinizing Hormone (LH) has a pivotal role in ovarian follicular development, ovulation, and luteal function. Whereas follicle-stimulating hormone (FSH) triggers follicular recruitment and growth, LH is critical for the final maturation of the oocyte, steroidogenesis, and ovulatory function. A fixed combination of recombinant FSH (r-hFSH) and recombinant LH (r-hLH), has proved to be an effective option in individualized controlled ovarian stimulation (COS), especially in women of advanced reproductive age, or those with diminished ovarian reserve (DOR), or poor responders. This review synthesizes current physiological, molecular, and clinical evidence towards the targeted use of r-hFSH:r-hLH, underlining its added value in enhancing ovarian response, oocyte quality, endometrial receptivity, and finally, IVF success rates.

Keywords: r-hFSH:r-hLH, ART (Assisted reproductive technology), COS (Controlled Ovarian Stimulation)

Introduction

Controlled ovarian stimulation (COS) is the cornerstone of assisted reproductive technologies (ART). Traditional protocols often favor FSH stimulation, underestimating the dynamic and essential role of LH. However, new data suggest that in specific subpopulations - particularly among older women,

poor responders, and hypogonadotropic patients - LH supplementation can significantly improve outcomes. Administration of a combined r-hFSH:r-hLH in a fixed ratio, simulates the natural gonadotropin environment better than FSH alone. Its use has the objective of not only maximizing follicular development but also to restore endocrine equilibrium and improve follicular-luteal function.

Physiological Basis of LH and FSH Action

FSH stimulates growth of granulosa cells, aromatase production, and estrogen production. LH, in turn, induces theca cell androgen production and, notably, induces LH receptor expression in dominant follicular granulosa cells - a key step in ovulation and luteinization [1, 2].

The two-cell, two-gonadotropin model emphasizes this synergy: FSH-dependent early follicle development is succeeded by LH-dependent late follicular maturation [3]. Granulosa LH receptor expression is induced under FSH influence and becomes obligatory during the preovulatory stage [4, 5].

Furthermore, LH is secreted in a pulsatile pattern, which is dependent on the frequency of GnRH pulses. According to Santoro et al [6] "just right" pulse frequency is critical for maximal LH and FSH release. Dysregulation - either hyposecretion or hypersecretion - will lead to follicular arrest, luteal dysfunction, or anovulation.

Clinical Implications of LH Deficiency and Supplementation

Functional LH deficiency may present in two modes: quantitative (low serum levels) and qualitative (ineffective LH action despite normal levels)[7]. Women with hypothalamic-pituitary dysfunction, advanced age, smoking history, or genetic receptor polymorphisms (e.g., in the FSHR or LHβ gene) may suffer from blunted LH activity.

During COS with GnRH antagonists, iatrogenic LH suppression often goes unrecognized, impairing oocyte quality and implantation potential. Excessive suppression (e.g., high antagonist doses) has been shown to be associated with diminished implantation and higher miscarriage rates [8].

Moreover, PCOS patients may also have elevated basal LH levels but reduced LH receptor sensitivity, where corresponding LH modulation is required. On the contrary, women with low LH levels, including those over 35 or poor responders, benefit from exogenous LH supplementation, which restores granulosa cell function and provides oocyte maturation.

Genetic Polymorphisms Influencing Gonadotropin Response

Polymorphisms modulating gonadotropin response can occur through influencing the affinity of gonadotropins to their receptors. The most studied polymorphisms include those in the follicle-stimulating hormone receptor (FSHR), luteinizing hormone/choriogonadotropin receptor (LHCGR), and the luteinizing hormone beta subunit (LHβ). The variants that are most significant are FSHR rs6166 (N680S), FSHR rs1394205 (−29), FSHB rs10835638 (c-211), LHCGR rs2293275 (S312N), and the LH beta variant rs1800447 [9]. These variations have an impact on receptor sensitivity and binding to ligands, hence altering ovarian response, oocyte quality, and clinical outcomes of COS procedures [10, 11].

Aside from receptor binding affinity, functional polymorphisms may alter intracellular signaling pathways. In vitro studies have proved that the LHCGR has the capacity to discriminate between LH and hCG activity, selectively stimulating anti-apoptotic signaling cascades, such as ERK1/2 and AKT, in granulosa cells [12]. Additionally, several polymorphic variants have been proved to be associated with alternative intracellular responses in granulosa cells, which may be responsible for heterogeneous ovarian stimulation outcomes [13].

Clinical Evidence Supporting the implementation of r-hFSH:r-hLH in ART

According to the findings of Arvis et al., the addition of LH to controlled ovarian stimulation (COS) protocols has been found to highly improve pregnancy rates, particularly among poor responders. [14]. Various studies have revealed that the addition of LH enhances oocyte quality, fertilization rates, and embryo viability [15-17]. Lehert et al. (2014) [18], supported that the addition of recombinant human follicle-stimulating hormone (r-hFSH) with recombinant human luteinizing hormone (r-hLH) improves ovarian response compared to r-hFSH alone, providing higher mature oocyte yields and improved clinical outcomes.

In addition, several clinical trials have confirmed that adding r-hLH reduces cancellation of cycles and generally increases overall success rates in assisted reproductive technology (ART) treatments [17, 19]. A number of studies illustrate the efficacy of this fixed combination regimen in specific patient populations, further validating the clinical use of LH supplementation during COS protocols [20, 21].

Effects on Endometrial Receptivity

In addition to its role in folliculogenesis, LH influences endometrial receptivity through regulation of steroid hormone synthesis. With LH regulation, granulosa and theca cells synthesize androgens and progesterone, controlling endometrial growth. Without adequate LH signaling, the endometrium may develop prematurely, falling out of alignment with embryonic development. There is some clinical evidence that co-treatment with r-hFSH and r-hLH can enhance endometrial thickness on the day of triggering final oocyte maturation compared with FSH alone, which could be beneficial for receptivity [22].

Furthermore, a systematic review demonstrates that when LH activity is supplemented from the beginning of stimulation, there can be reduced progesterone levels upon receiving hCG injection versus regarding protocols that do not include LH supplementation; though this is not always reported [23]. Direct evidence that fixed r hFSH:r hLH is certainly avoiding excessive progesterone elevation or offering optimal luteal support synchronization with embryo transfer is not yet present.

Personalized Medicine and the Future of COS

The efficacy of this gonadotropin combination therapy emphasizes the importance of individualized COS protocols. Age, ovarian reserve, BMI, smoking, and gonadotropin receptor polymorphisms must all be considered. Younger patients may also benefit in specific contexts, especially when functional gonadotropin deficiency is suspected.

With aging, receptor sensitivity declines and LH quality deteriorates. Women over the age of 35 often have <50% receptor activity, necessitating individualized gonadotropin combinations.

Conclusion

The combination of r-hFSH and r-hLH provides a physiologically correct and clinically proven strategy in controlled ovarian stimulation. By replicating the natural interplay of FSH and LH, it enhances follicular development, oocyte competence, and endometrial receptivity. Its targeted use in women with diminished ovarian reserve, advanced reproductive age, or functional LH deficiency improves the chances of successful IVF outcomes. Incorporating this approach into individualized treatment regimens represents a step forward in reproductive medicine, aligning clinical intervention with endocrine physiology.

Authors' Contributions

E.D, E.M, N.V: Conduct, Data collection and analysis,

E.D: Manuscript writing E.M, N.V: Manuscript editing

All authors have read and agreed to the published version of the manuscript.

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