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LH Supplementation in Ovarian Stimulation for IVF: The Individual, LH Deficient, Patient Perspective

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Abstract
The availability of recombinant follicle-stimulating hormone (FSH) and luteinizing hormone (LH) opens an opportunity to individualize ovarian stimulation. While the need for FSH in ovarian stimulation is universal, a question remains whether exogenous LH is beneficial. Previous population-based research showed that added LH is indicated in elderly and in profoundly LH depressed patients. This commentary explores potential individual patient parameters that may hint that this specific individual may prospectively need supplemented LH, irrespective of her age or experience from previous cycles. Specifically, it is suggested that in an antagonist protocol, the degree of LH recovery 24 h post first GnRH antagonist injection can identify those patients who may benefit from added LH. In addition, rising LH during the first 5 days of stimulation may predispose patients to a sharp LH drop following the first GnRH antagonist dose, and the need for added LH.

Introduction

In the natural ovulatory cycle, the pituitary secretes 2 glycoprotein hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In the follicular phase, FSH is the main regulator of mono-follicular development. FSH rises in the late luteal and early follicular phases to induce follicular growth. LH is responsible for steroidogenesis by the growing follicles. When a dominant follicle attains enough granulosa cell mass, the rising estradiol it secretes negatively affects the pituitary, FSH secretion is inhibited, and a single follicle continues to grow, until mid-cycle LH and FSH surges trigger ovulation.

Ovarian stimulation for IVF aims at achieving multiple mature oocytes. Exogenous FSH that overrides the intrinsic regulatory mechanism accomplishes this goal. Do we need to supplement the follicular phase with LH? Over the past few decades, a large body of research was published to answer this question. However, no clear answer is available so far, probably due to the population-based design of the studies performed. Consequently, we may conclude at this point that elderly patients and those with excessive LH suppression may benefit from supplement-

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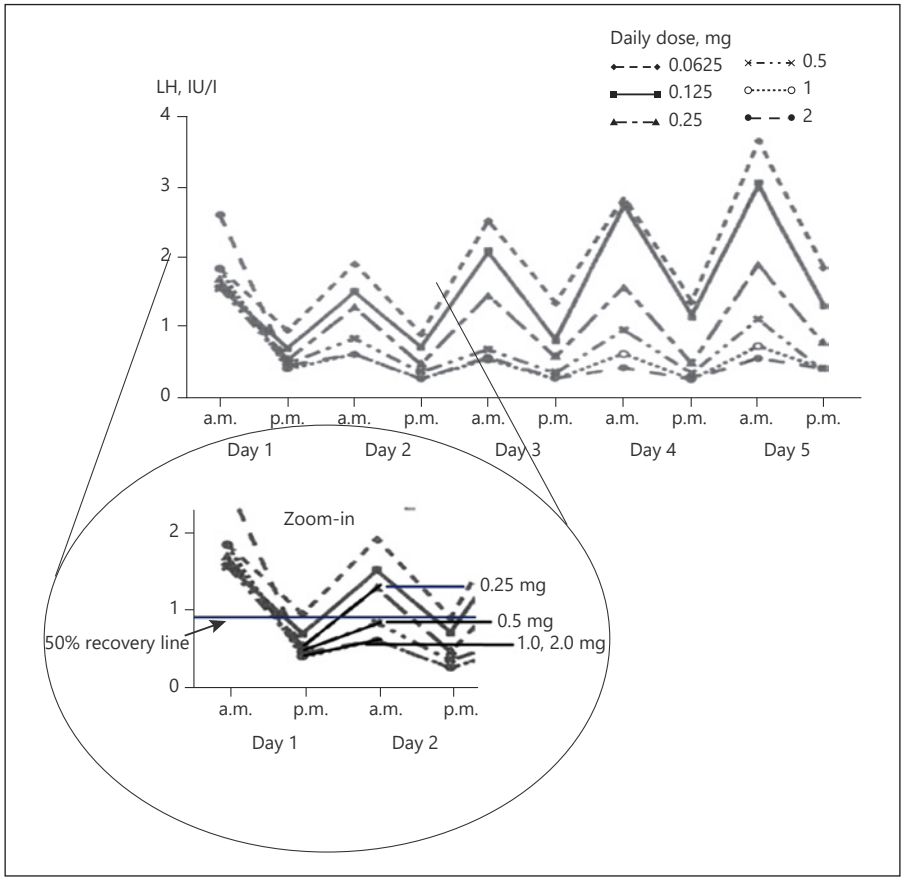

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Fig. 1. Reproduces with permission from the ganirelix dose-finding study (1998): Mean LH just before GnRH antagonist injection was about 1.8 IU/L for most patients; therefore, the 50% LH recovery line was set on 0.9 IU/L. In all 6 dose groups, LH as measured 8 h after dosing fell below that line. In both high-dose groups (1.0 mg and 2.0 mg) LH hardly recovered 24 h post dosing (just before the second GnRH antagonist injection). These 2 groups were prematurely terminated due to bad reproductive outcome. The 0.5 mg dose group nearly touched the 50% recovery line, while the chosen dose (0.25 mg) group recovered nicely, way above the 50% recovery line. LH, luteinizing hormone.

ed LH [1, 2], as well as patients with hypo-response to ovarian stimulation [3]. The purpose of the current commentary is to depart from the population-based approach and try to explore potential individual patient parameters that may hint that this specific individual may prospectively need supplemented LH, irrespective of her age or performance in previous cycles.

Lessons from the Ganirelix Dose-Finding Study

Although published more than 20 years ago, the ganirelix dose-finding study [4] is revisited with the emphasis on a key endocrine factor: recovery of LH level 24 h after first GnRH antagonist injection. At the outset, we must remember that the 2 highest dose (1 and 2 mg) groups in that study had to be prematurely terminated because of bad reproductive outcome. If we take a closer look at the data, it is evident that all doses used caused comparable LH suppression when measured 8 h post first injection (Fig. 1). LH in the low-dose groups fully recovered to its pre-dosing level 24 h earlier. In contrast, LH in the high-dose groups was still suppressed 24 h after dosing. Bases on Figure 1 ("zoom-in" insert), it seems that more than 50% LH recovery post first dosing is the threshold between the higher and the lower doses used. The chosen dose (0.25 mg) offered the best balance between premature LH rise suppression, good reproductive outcome, and almost full recovery to the pre-dosing level.

Huirne et al. [5] documented the importance of LH change and showed that the magnitude of LH drop during antagonist treatment is associated with low pregnancy rate, with no relevance to the actual concentrations. Hence, subjects with profound suppression of LH production, irrespective of the antagonist dose, did not achieve pregnancy. The concept of change over time as a significant hormonal milieu determinant, rather than the level at a given time point, was previously reviewed [6, 7].

Do all pituitaries respond the same to a given GnRH antagonist dose? Formal data on LH response scatter to the 0.25 mg GnRH antagonist dose are not available, but it is reasonable to speculate that it should obey a bell

shape. Consequently, some patients may hypo-respond and are at the risk for premature LH rise and premature luteinization. However, some patients may hyper-respond to the 0.25 mg dose and behave as if they were exposed to a higher GnRH antagonist dose. These patients may benefit from added LH, in order to secure good reproductive outcome.

Can we identify these patients? Yes, if we follow the ganirelix dose-finding study data. If a patient fails to recover her LH level 24 h post dosing, at least by 50% of the pre-dosing level (Fig. 1), she can be identified as a GnRH antagonist "hyper-responder," and this particular individual may need exogenous LH to compensate her pituitary oversensitivity to the GnRH antagonist. The difference is LH recovery 24 h after dosing is a key point in the magnitude of pituitary response to the GnRH antagonist. Studies that described dose-dependent antagonist pharmacodynamics and pharmacokinetics indicate that the immediate response to all doses of GnRH antagonists is a drop in LH levels, which is similar in its extent among all doses. However, a large difference in LH levels is observed for the pituitary recovery 24 h later [8].By this definition, we depart from the population-based approach and adopt a novel, patient-specific endocrine event that can distinguish between individuals who need or do not need supplemented LH during ovarian stimulation.

GnRH Antagonist Hyper-Responders

The actual percentage of GnRH antagonist hyper-responders in the general population was never given by the pharma industry; however, it is of paramount importance if we seek to individually target these patients, as they may benefit from supplemented LH. In an effort to shed some light on this issue, we have conducted a small study aiming at exploring the prevalence of GnRH antagonist hyper-response in IVF patients [9]. We included 50 "model" IVF patients. Patients were stimulated with a recombinant FSH preparation. On the morning of the fifth or sixth stimulation day, a blood sample was taken, after which a standard GnRH antagonist dose (0.25 mg) was given, establishing the pre-dosing LH level. A repeated blood sample was taken 24 h later, establishing LH recovery. If LH recovery was more than 50% of the pre-dosing level, the patient was identified as a "GnRH antagonist normal responder," and stimulation was continued without change. If LH recovery was less than 50% of the pre-dosing level, the patient was identified as a "GnRH antagonist hyper-responder" and was supplemented with recombinant LH (150 IU daily) until the trigger day. Twelve subjects (26.1%) were defined as "GnRH antagonist hyper-responders." In this group, the mean LH level after the first GnRH antagonist injection was 37% of the LH level 24 h earlier. Thirty-four subjects (73.9%) were defined as "GnRH antagonist normal responders." In this group, the mean LH level after the first GnRH antagonist injection was 70% of the LH level 24 h earlier. Administration of exogenous LH to "GnRH antagonist hyper-responders" led to an increase in E_2 increment per oocyte retrieved. Clinical outcomes (number of retrieved oocytes, fertilization rate, number of embryos obtained, and pregnancy rate) were comparable between the 2 groups. Importantly, high LH levels, just before the first antagonist injection, may predispose a subject to a sharp decrease in LH 24 h later ("GnRH antagonist hyper-responder").

LH Levels during Ovarian Stimulation

From the abovementioned study, we have concluded that pituitary susceptibility to GnRH antagonist increases in a direct relation to LH level just before first injection. Therefore, a closer look at LH changes during ovarian stimulation is needed.

The follicular phase endocrine characteristics during ovarian stimulation with GnRH antagonist co-treatment were thoroughly studied. Focusing on LH levels during the first half of the follicular phase, a sharp drop in its serum level was demonstrated between cycle day 2 and day 6 [10]. On cycle day 2, mean LH level was 5 IU/L, dropping to 1.7 IU/L 4 days later, before GnRH antagonist was given. This study examined selected, good prognosis patients obeying very restrictive criteria. Similar results were reported in another publication, using comparable inclusion criteria [11]. In summary, the "normal" response to 5 days of gonadotropin stimulation is a drop in the LH level.

While the above studies represent a subset of "model" patients, there is an interest to investigate if these findings hold true for "real-world" patients. Based on our previous publication, only 37% of the "real-world" patients meet the inclusion criteria as defined by 9 major clinical trials [12]. Importantly, if we seek individual patient perspective, attention must be given to those individuals whose LH level increases during the first half of the follicular phase, before a GnRH antagonist is given. An increase in LH level (rather than the expected decease), during the first half of ovarian stimulation, could be associated with

a sharp decrease in LH immediately after first GnRH antagonist injection, lack of LH recovery 24 h later, and a need to compensate with LH supplementation. Therefore, we set to assess the frequency of this "abnormal" LH dynamics in unselected IVF patients, in other words, to determine the percentage of patients demonstrating an increase in LH serum level from stimulation start day to mid-follicular phase, just before first GnRH antagonist injection.

We included 165 consecutive patients treated with a GnRH antagonist-based ovarian stimulation protocol [13]. Of the 165 patients, in 110 patients (67%), an LH decrease was documented between day 1 and day 5 of ovarian stimulation, as expected. In 55 patients (33%), an increase in LH was noted during the same period. So far, it was not shown that a decrease or an increase of LH levels on day 5, before the start of GnRH antagonist, has an impact on the ART outcome; therefore, further research in that line is warranted.

Two significant players govern pituitary LH secretion during ovarian stimulation: E_2 and ovarian gonadotrophin surge attenuating factor (GnSAF) [14, 15]. In the natural ovulatory cycle, a rapid rising E_2 level (to about 1,000 pmol/L) secreted by the dominant follicle is the cue to pituitary LH surge and ovulation. In most patients, comparable E_2 levels are reached after 5 stimulation days; however, LH secretion is decreased given the dominant influence of GnSAF secreted by the developing follicles. This hormonal balance if offset in 2 situations: excessive E_2 (a patient with excessive ovarian response) or diminished GnSAF secretion (a patient with diminished ovarian response). Indeed, our study hints that LH rising levels may reflect either over- or diminished ovarian response.

Finally, routine LH measurement does not necessarily reflect residual LH bioactivity in various clinical conditions with increased and decreased gonadotropin secretion [16]; however, from the clinical point of view, ART cycles are conducted by the available measurements. Each ART center is advised to verify the reproducibility of its LH measurement method.

Summary

In the "model" patient population, about 25% of the patients hyper-respond to the GnRH antagonist and may benefit from added LH. In the "general, real-world" patient population, 33% of the patients have increased LH level during stimulation, before first GnRH antagonist injection and are at risk of hyper-response to the antagonist and, therefore, may benefit from added LH. The latter population comprised mainly gonadotropin hyper- and hypo-responders.

The practicing physician may wonder what are the chances that the next patient entering his/her office will benefit from supplemented LH. The current commentary may not only give a good estimate but also add to the physician's toolbox simple measures if an exact estimate is needed.

Conflict of Interest Statement

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