Journal of Assisted Reproduction and Genetics
https://doi.org/10.1007/s10815-024-03033-9

COMMENTARY

LH supplementation in IVF: human nature, politics, and elephants in the room

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Received: 20 November 2023 / Accepted: 12 January 2024

Abstract

Luteinizing hormone (LH) is present throughout the natural follicular phase. However, the debate is still not settled on whether LH is needed during ovarian stimulation in IVF. This commentary looks at the evolution of this debate, mentioning three elephants in the room that were ignored by the Pharma industry, professional organizations, and clinicians alike:

1. The different endocrinology between the long agonist and the antagonist protocols.
2. The fixed dose of the two most widely commercially available antagonist preparations, namely cetrorelix and ganirelix.
3. The fact that most research in this area uses population-based criteria, ignoring endocrine parameters.

Individual genetics of the LH receptor gene may also serve to individualize LH needs during stimulation; however, the jury is still out regarding this approach.

Conclusions Individual endocrine and genetics parameters may shed meaningful light on the question of LH supplemental during ovarian stimulation.

Keywords LH · IVF · Controlled ovarian stimulation · GnRH agonist · GnRH antagonist

The topic of LH supplementation has been a subject of multiple research studies and opinion papers for decades. During the last decade of the last century, the long GnRH agonist protocol reigned the IVF scene. However, with the advent of recombinant FSH products, a departure from the previous hMG formulations occurred, leading to a notable decrease in LH bioactivity. Unlike the hMG products, which inherently contained sufficient LH support, the newer recombinant FSH-only products lacked this essential component. This shift in ovarian stimulation protocols, specifically the move away from hMG, coincided with the emergence of concerns regarding LH supplementation, a phenomenon not observed in the earlier phases of ovarian stimulation history. When the pharmaceutical industry developed recombinant FSH, it conveyed the message that LH is not needed during ovarian stimulation, despite LH playing a crucial role in the natural ovulatory cycle. This message was supported by the fact that, in the long agonist protocol, LH is indeed low but remains quite stable during ovarian stimulation. Under these circumstances, the cycle outcome is not influenced by follicular phase LH levels [1]. This discrepancy likely arises from the inadequate reflection of LH bioactivity by its immunoreactivity, primarily attributable to its very short half-life. Notably, the efficacy of LH supplementation is not mirrored in serum LH levels but rather manifests itself in its influence on follicular steroidogenesis.

When the GnRH antagonists came to the market in the early 2000s, the ruling theme was that the same stimulation rules are still applicable, e.g., FSH-only stimulation

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is the way to go. This approach ignored the fact that the endocrinology of the GnRH antagonist protocol is markedly different [2]: elephant in the room number 1.

In contrast with the long agonist protocol, LH concentrations fluctuate in the GnRH antagonist protocol as documented by Borm and Mannaerts [3], who demonstrated significant inter-patient variability in the LH response to ganirelix on day 6 and on trigger day. The degree of fluctuation is related to the individual pituitary response to the uniform recommended dose (0.25 mg a day). Surprisingly, both GnRH antagonist preparations came to the market with the same recommended dose for all patients. While considerable research efforts were invested in precisely defining the individualized FSH dose required for specific patients, it is notable that, by the early 2000s, IVF providers began to adopt the pharmaceutical industry's approach of "one dose fits all" for the commercially available GnRH antagonist preparations. However, this approach may not fully account for variations in the pituitary gland function [4–6], akin to the acknowledged differences in other reproductive organs such as the ovaries (elephant in the room number 2).

In line with the above, professional organizations, including ESHRE, ASRM, MEFS, and others, did not ask for scientific evidence for the "one size fits all" dictum for the GnRH antagonist protocol. In fact, 20 years after the antagonists were introduced, ESHRE recommends the use of "gonadotropins" in both the antagonist and long agonist protocols without specifying the choice of gonadotropins—a "pragmatic" approach [7].

While recombinant LH was developed primarily to be used as an ovulatory trigger [8], which never gained traction, only recently, the focus shifted to the use of LH during ovarian stimulation. Correctly, the term "relative LH deficiency" was coined to describe those patients who might need supplemental LH [9]. However, the question of how to define the individual patient in need of supplemental LH has been neglected, despite proposals from reproductive endocrinologists to improve our understanding and individual clinical assessment of pituitary reserve and function.

In the era of personalized medicine, one would assume that individual endocrine parameters should be the focus of research addressing the individual need for supplemental LH. Translational research is needed to identify individual patient-specific endocrine profiles associated with the highest benefit of LH supplementation. Up until now, most research has taken the population-based RCT approach, i.e., focusing on age groups ([10–20]). Why? Perhaps because the population-based RCT is easier to perform (simple inclusion and exclusion criteria, easy recruitment), with a good chance to be accepted for publication. Human nature tends to use known paths, rather than to blaze new trails that can lead to a dead-end. Naturally, these RCTs produced multiple meta-analyses [21] with a weak message that added LH is somewhat beneficial for advanced maternal-age patients (35–40). This conclusion does not allow us to address the needs of a specific patient of any age.

The ganirelix dose-finding study [2], in which recombinant FSH was used for stimulation, sheds some light on the endocrinology of the GnRH antagonist protocol. Two facts stand out:

1. The higher the serum LH, the deeper the drop following GnRH antagonist dosing.
2. Clinical pregnancy rate is positively associated with the degree of LH recovery 24 h post-GnRH antagonist dosing.

These, or similar endocrine criteria, may lead to more meaningful research and conclusions regarding the individual need for added LH. However, this is a long and winding road, much more complicated than the easy-to-perform population-based RCT (elephant in the room number 3).

Another direction for individualization of the LH supplementation question is the impact of specific genetic variations, or polymorphisms, on the effectiveness of gonadotropin treatment. Pharmacogenetics studies emphasize the influence of individual genetic differences on controlled ovarian hyperstimulation (COH) outcomes, paving the way for personalized therapies tailored to patients' genetic profiles. The action of LH is intricate, involving various factors, including LH and its receptor polymorphisms. Besides mutations in the LH receptor gene (LHCGR), certain LH and receptor polymorphisms have been linked to reduced fertility due to diminished natural gonadotropin activity or resistance to ovarian stimulation, leading to lower-than-expected egg yields [22, 23]. It is noteworthy to mention that, in some cases with LH receptor polymorphisms, the surrogate product of LH, namely hCG, whether recombinant or biologically purified, could be considered a viable solution in the armamentarium of the "modern" reproductive endocrinologist striving for a more personalized approach in ART stimulation. However, the prevalence of these specific genetic variations in ART remains unknown because they are not routinely tested. The analysis of single nucleotide polymorphisms (SNPs) holds promise for tailoring COH protocols to individual patients in the future. While accumulating data suggest that ovarian responses to COH are influenced by various polymorphisms, identifying optimal biomarkers and evaluating test efficacy remain challenges. Several studies have explored the impact of LH gene polymorphisms on IVF outcomes, yet the pharmacogenetics approach to LH dosing requires further consolidation. Ultimately, the most accurate COH test will likely combine patient-specific

epidemiologic factors and biological characteristics with genetic markers [24]. COH-pharmacogenomics research holds the promise of enabling individualized ovarian stimulation protocols, offering hope for personalized treatments in assisted reproduction.

In summary

The question of the need for added LH during ovarian stimulation still awaits evidence-based answers, while upfront tackling the elephants that are still left in the room.

Author contributions JC: contributed in writing the manuscript; AMQ: contributed in writing the manuscript; SK: conceived the basic ideas and contributed in writing the manuscript. All authors read and approved the manuscript, and all data were generated in-house, and no paper mill was used.

Data availability Not applicable

Declarations

Ethical approval Not applicable for a commentary paper.

Consent to participate Not applicable for a commentary paper.

Consent for publication Not applicable for a commentary paper.

Competing interests The authors declare no competing interests.

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