Luteinizing hormone's critical role in ovarian stimulation

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In assisted reproductive technologies (ARTs), refining ovarian stimulation (OS) protocols has long been seen as a crucial step for optimizing outcomes such as oocyte retrieval, fertilization, and, ultimately, successful pregnancy. Traditionally, the follicle-stimulating hormone (FSH) component of human menopausal gonadotropin (hMG) was seen as the primary agent of successful ovarian response in OS protocols. Originally, luteinizing hormone (LH) bioactivity contained in hMG preparations was even seen as a potential contaminant, which could be deleterious for OS outcome. Later, however, the role of LH has gained significant attention, being seen as beneficial in specific patient populations beyond those with hypogonadotropism. This article explores the evidence supporting the incorporation of LH into OS protocols. Attention is focused on the differential molecular actions of LH and human chorionic gonadotropin (hCG) on its sole receptor, the source of LH bioactivity in the existing commercial products (1), and clinical evidence supporting its role in certain types of protocols and patient types.

HISTORICAL PERSPECTIVE AND EVOLUTION OF GONADOTROPIN PREPARATIONS FOR IN VITRO FERTILIZATION

Understanding the historical context of gonadotropin therapy provides valuable insights into the current use of LH in OS. The development of gonadotropin preparations has evolved significantly over the past century, from crude animal extracts to highly purified urinary and recombinant products (2). The American Society for Reproductive Medicine outlined this progression of gonadotropin therapy, noting that the advent of recombinant LH (rLH) has allowed for more precise and effective stimulation protocols (3).

In the early days of ART—then known as in vitro fertilization (IVF)—only one commercially available gonadotropin product was available, an hMG preparation. This was derived from the urine of menopausal women and contained both FSH and LH bioactivities. Although effective, the original product was not ideal. For one, because the original hMG preparation was minimally purified—it contained many contaminant proteins—it needed to be administered by intramuscular injections, which were painful and cumbersome. A "cleaner"—that is, more highly purified—preparation was, thus, desired.

A second concern was the LH activity that hMG contained. At the time, there was concern about a possible negative effect of LH bioactivity contained in hMG and ensuing androgen production on oocyte quality (4, 5). Several reports from the time highlighted this issue: high androgen/estrogen ratios were associated with less healthy follicles. Elevated LH levels during stimulation were reported to be associated with poorer ART outcome (6). Punnonen et al. (7) reported that lower cleavage rates occurred when high LH levels were present 12 hours or more before the LH surge. Homburg et al. (8) studied outcomes of gonadotropin-releasing hormone (GnRH) pump treatment in patients with polycystic ovary syndrome (PCOS) and found that those who ovulated but did not conceive had higher basal LH levels, as did those who miscarried. Another study (9) examined 193 women with ovulatory cycles trying to conceive naturally and divided them into two groups on the basis of their LH level during the follicular phase (mostly on cycle days 7–9). Those with an LH level of >10 IU/L conceived less often (67% vs. 88%) and miscarried more often (65% vs. 12%) than those with an LH level of <10 IU/L. Taken together, there was real concern that the LH in contained in HMG could impair OS and, in turn, ART outcome. These observations led to generate the expectation that eliminating LH from OS preparations wound improve ART outcomes. Discussions at the time acknowledged that endogenous LH may be the culprit; however, the belief was that giving more LH through hMG would only make matters worse. With the benefit of hindsight, practitioners were too quick to note the association—high LH and diminished outcomes—and demonstrate a causative link (5). It now seems that these negative findings were likely due to the endogenous LH because no GnRH analogues were available during the early years of IVF. Given the half-lives of LH and the known pharmacokinetics of hMG, it is unlikely that high LH levels stemmed were from the medication. Rather, in these pre-GnRH analogue times, it was more likely that a high LH level represented patients who presented premature LH surges or those with high endogenous LH production such as patients with PCOS.

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A third concern about the original hMG preparation was to secure an adequate supply. It took all the urine from 60,000 nuns annually to fill the hMG need in 2000 (10). Because IVF was becoming even more widespread, the practical difficulty of collecting enough urine for the worldwide IVF volume became a real concern. The newly discovered process of manufacturing recombinant DNA techniques was a welcome solution that was promptly investigated and adopted (11).

Taken together, pharmaceutical firms were motivated by the following three imperatives for developing new gonadotropin products: purer product available for subcutaneous injection; less LH activity; and easier to produce in large quantities (2). Consequently, new gonadotropin formulations were developed (3, 12): these included purer versions of urinary products and novel recombinant versions of both FSH and LH. The resulting products could be injected subcutaneously, and the recombinants could be produced with unlimited supply. Table 1 lists the various gonadotropins that have been commercially available.

The pharmaceutical industry succeeded in producing purer FSH preparations, which were generally effective in OS (11). However, the important role of LH in normal folliculogenesis was underappreciated at the time. Erroneous conclusions about the apparent negative impact of LH on healthy folliculogenesis led many practitioners to prefer gonadotropin preparation devoid of LH activity. As we will review, for certain patient populations, this is detrimental, for example, women with hypogonadotropism (13). We have had to relearn that some level of LH activity is essential and is, on occasion, deficient in routine IVF stimulations. Hindsight suggests that the concerns about elevated LH activity were misplaced and likely stemmed for poorer outcomes following suggest they poorly timed triggering or shifting of the window of receptivity. We will review the reasons, evidence, and strategies that flow from this rediscovered understanding of LH's critical role. As the negative effect of omitting LH activity in some ART OS in certain situations and patients became evident, products were developed that offered a means to add back some LH activity, typically in the form of newly developed highly purified hMG or rLH.

BIOLOGY OF LH AND ITS ACTIONS

Gonadotropin hormones (FSH, LH, and hCG) are heterodimeric glycoprotein hormones with alpha and beta chains whose biologic action depends heavily on the degree and type of glycosylation. Moreover, in vivo, there are different isoforms of the same gonadotropins with different biologic actions (14). Consequently, to judge the potency of gonadotropins, bioassays are necessary. Historically, the first bioassays did not and could not distinguish FSH from LH and defined 1 IU of gonadotropin as the minimum amount that caused ovarian hyperemia in a mouse model (2). Later, when FSH and LH could be physically separated from one another, it was possible to develop distinct bioassays for both FSH and LH (2). Full reviews of this topic are available (15, 16). With the advent of recombinant versions with fixed isoform patterns, it is now possible to use actual hormone weight instead of bioassay to gauge hormone content (12).

The use of bioassays has revealed that the biologic activity of LH can vary considerably. This discrepancy underscores the importance of LH's bioactivity in both physiological and clinical contexts. Variations in LH bioactivity, as demonstrated through bioassays, have direct implications for fertility treatments, where precise modulation of LH levels is crucial for optimal outcomes (17, 18).

A single receptor (LHCGR) binds both LH and hCG

For some time, the fact that both LH and hCG bind to the same receptor (luteinizing hormone/choriogonadotropin receptor [LHCGR]) was taken to mean that they were largely interchangeable in clinical application. However, detailed analysis of the intracellular effects demonstrates significant differences when LH and hCG bind the same receptor (reviewed

TABLE 1

Gonadotropin preparations used in assisted reproductive technology treatments.

Type of gonadotropin	FSH activity	LH activity	Brand names
Human derived			
hMG	75 IU	75 IU	Pergonal, Humegon, Menogon, and Repronex
hMG	75 IU	25–25 IU	Normegon and Pergogreen
HP hMG	75 IU	75 IU	Menopur and Meriofert
HP FSH	75 IU	<1 IU	Metrodin and Fostimon
HP FSH	75 IU	<0.1 IU	Metrodin HP and Bravelle
Recombinant			
rFSH α	5.5 μg (FSH 75)	0	Gonal F
rFSH β	75 IU	0	Follistim and Puregon
rFSH α (corifollitropin)	100–150 μg	0	Elonva
rFSH δ	12–72 μg	0	Rekovelle
rLH α	0	75 IU	Luveris
Chorionic gonadotropins			
hCG	CG 250–5,000 IU	CG 250–5,000 IU	Profasi, Gonasi, Novarel, Pregnyl, and Choragon
rhCG	CG 250 μg	CG 250 μg	Ovidrel and Ovitrelle

Note: FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; HP = highly purified; rFSH = recombinant follicle-stimulating hormone; rLH = recombinant luteinizing hormone.

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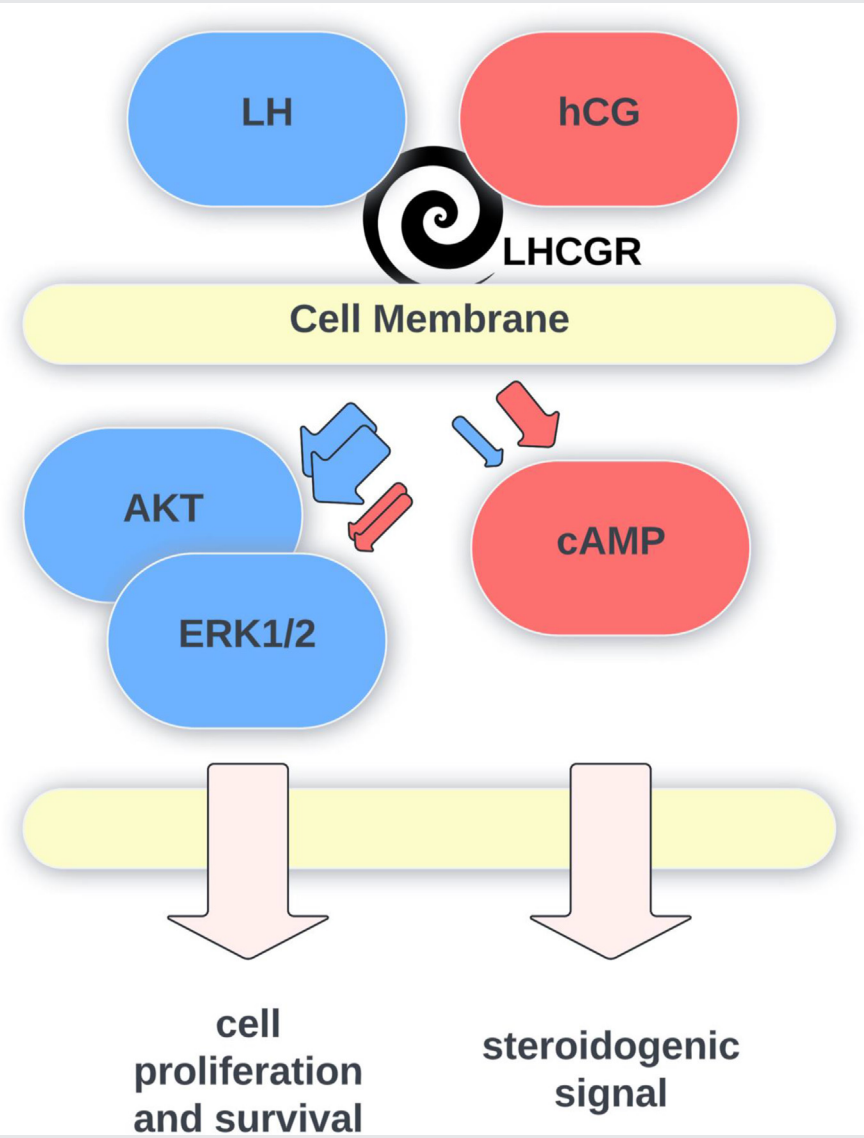
in the following). For this reason, it is now important to distinguish LH from hCG in gauging treatment effects. Therapeutic strategies need to be grounded in the unique and distinct bioactivities of LH and hCG on the outcomes of ART, rather than a general measure of "LH activity."

Several studies consistently demonstrate that LH and hCG, despite acting on the same receptor (LHCGR), trigger distinct intracellular signaling pathways that lead to different physiological outcomes (Fig. 1) (19). Luteinizing hormone predominantly activates the ERK1/2 and AKT pathways, promoting cell proliferation and survival, whereas hCG is more potent in generating cAMP and supporting steroidogenesis, particularly progesterone (P4) production during pregnancy (19, 20). Because of these differences, LH tends to act faster than hCG in promoting intracellular responses. For example, maximal activation of cAMP occurs more quickly with LH (within 10 minutes) than with hCG (which takes approximately an hour). Reports show that hCG is more potent in sustaining long-term hormonal activity because of its longer half-life and higher efficacy in cAMP production (19).

Research confirms that hCG exhibits stronger β-arrestin recruitment and cAMP production, making it more effective in prolonged receptor activity and steroidogenic responses (21). Meanwhile, LH shows a greater ability to activate non-

FIGURE 1



Preferential luteinizing hormone (LH)–induced and human chorionic gonadotropin (hCG)–induced signals in ovarian granulosa cells. Although hCG was more potent than LH in inducing intracellular cAMP increase and steroidogenic signals, LH predominantly activates ERK1/2- and AKT-mediated proliferative and antiapoptotic signals. (Adapted from Casarini et al. (19)).

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cAMP pathways, particularly those involved in (21) proliferation and cell survival, which are essential for follicular development and ovulation (19, 21). These findings are particularly relevant for clinical applications in reproductive medicine, where understanding the specific roles and mechanisms of LH and hCG can optimize fertility treatments and improve outcomes (21). The earlier view that these hormones are interchangeable is now seen as an oversimplification because they clearly activate different signaling pathways leading to their unique biologic effects.

Advances in molecular biology have provided deeper insights into how LH influences follicular development at the genetic level. Nair et al. (18) explored the role of LH/hCG receptor-specific messenger RNA (mRNA) binding proteins in regulating receptor expression in human ovarian granulosa cells. The study found that LH receptor mRNA undergoes transient down-regulation after the LH surge, a process mediated by specific mRNA binding proteins. This posttranscriptional regulation suggests that LH plays a complex role in follicular dynamics, influencing both receptor expression and oocyte maturation. The study demonstrated that LH receptor expression decreases after hCG administration, a process mediated by the increased binding activity of LRBPs, leading to mRNA degradation. This regulation is critical for preventing overstimulation and ensuring that follicles are not prematurely luteinized.

The evidence suggests that LH contributes to several critical processes during OS, including the prevention of premature luteinization, support of final oocyte maturation, and improvement of endometrial receptivity. The mechanisms by which LH exerts its effects are multifaceted, involving both direct stimulation of androgen production and modulation of gene expression through mRNA binding proteins. Clinically, these mechanisms translate into improved follicular responses and potentially higher pregnancy rates, particularly in patients who may have suboptimal responses to FSH alone (10, 22).

Luteinizing hormone plays a crucial role in the later stages of follicular development, supporting theca cell function to produce androgens, which are then aromatized to estrogens in granulosa cells under the influence of FSH. This 2-cell, 2-gonadotropin model underscores the synergistic action of FSH and LH in normal follicular development and oocyte maturation. Additionally, LH is essential for the selection of the dominant follicle, triggering ovulation, and ensuring luteinization of the follicle (23). The LH surge triggers the resumption of meiosis in the oocyte, leading to ovulation. In this context, LH ensures the proper timing of oocyte release and the subsequent formation of the corpus luteum, which is essential for P4 production and the maintenance of early pregnancy.

A key aspect of LH's role in OS protocols is its distinct function compared with hCG. Gromoll et al. (24) highlighted the unique interactions between LH, hCG, and their receptor, particularly in cases where the receptor is structurally altered. Their study revealed that although hCG can stimulate testosterone production and spermatogenesis in a mutant receptor lacking exon 10, LH could not. This finding emphasizes the specific role of LH in certain physiological contexts, which cannot be fully replicated by hCG (25).

This differentiation is particularly relevant in OS protocols where hCG has traditionally been used to trigger ovulation. However, the use of LH can offer benefits in situations where precise control over the timing and nature of follicle maturation is needed. For instance, in patients with low ovarian reserve or in those with specific receptor mutations, adding LH can help ensure that the follicles reach full maturity and that ovulation occurs in a more physiologically synchronized manner (23).

Choi and Smitz (2015) (26) explored the clinical implications of mutations in the LH/hCG receptor, noting that these can lead to gonadotropin resistance and a range of reproductive issues. Their research suggests that in some cases, traditional stimulation protocols that rely solely on FSH and hCG are not sufficient to achieve optimal outcomes. By adding LH, it is possible to overcome some of the limitations associated with these mutations, ensuring that the follicles respond appropriately to stimulation (26). A recent study reported that in ART cycles using low-dose hCG in a ration as per clinic routine OS protocol (27), the presence of gonadotropin receptor polymorphisms is not associated with ART outcome (28).

The physiological role of LH in follicular development

The synergistic role of LH with FSH in follicular development is crucial, especially in cases where FSH alone may be insufficient for optimal estradiol (E2) production and follicle maturation (22, 29). Furthermore, the administration of low-dose LH activity via hCG alone after follicle selection has been shown to support continued follicular development in the late stages of stimulation, potentially reducing the risk of ovarian hyperstimulation syndrome (OHSS) by sustaining the growth of selected follicles without recruiting new follicles into growth (30). A meta-analysis confirmed that although FSH alone may result in a higher number of oocytes, the addition of LH improves the quality of the oocytes and embryos, supporting the personalized approach to gonadotropin supplementation (10). Additionally, LH supplementation may help achieve better synchronization of follicular waves and improve clinical outcomes such as implantation and pregnancy rates in specific patient populations. These benefits suggest that LH addition is a valuable component in personalized OS protocols aimed at improving the chances of successful conception and live birth in ART (31).

CLINICAL OBSERVATIONS OF LH'S EFFECT IN OS

In natural cycles, FSH recruits follicles into growth, all but one of which undergoes atresia because of decreasing FSH levels. The continued growth of the dominant follicle is supported by increasing LH levels, which bind to the newly acquired LH receptors on the granulosa cells.

In OS, the provision of high levels of FSH throughout stimulation forestalls attrition, and the need for LH is not as

evident. However, the addition of LH to OS protocols has shown benefits, at least in certain groups. Studies indicate that combining LH with FSH can improve pregnancy rates, particularly in women aged 36–39 years and those with low endogenous LH levels and enhance the production of high-quality embryos (10, 32). In cases of profound pituitary suppression due to GnRH analogue use, the addition of LH can restore the hormonal balance necessary for successful outcomes in IVF (22). Studies also suggest that in women with low endogenous LH levels or poor ovarian response, the inclusion of LH in stimulation protocols improves follicular development and increases E2 production, which is crucial for endometrial receptivity and successful implantation (29, 33). Moreover, LH receptors are present in the endometrium (34) where it could have effects independent of the sex steroids.

Moreover, clinical studies have shown that the inclusion of LH activity in OS protocols can improve outcomes in specific patient populations, such as those with poor ovarian response, advanced maternal age, or previous cycle failures. The rationale is that LH supplementation can enhance the intrafollicular androgen environment, which is necessary for the proper development of follicles and the subsequent maturation of oocytes.

Meta-analyses have further clarified the role of LH in OS. A systematic review by Mochtar et al. (35) concluded that LH supplementation is particularly beneficial for women with diminished ovarian reserve (DOR) or those who are older, supporting the use of rLH in tailored stimulation protocols. These findings are consistent with other reviews that have highlighted the selective benefits of LH, particularly in patient subgroups with specific endocrine profiles (35).

There are several lines of evidence indicating LH's critical and beneficial role in oocyte growth and competence:

- Women with hypothalamic hypogonadism (including Kallman syndrome) struggle grow follicles in response to FSH stimulation and cannot produce normal levels of E2, unless LH activity is also provided (5, 36–38). Moreover, their eggs do not function well if only FSH was provided. This suggests that LH is necessary for follicular steroidogenesis and oocyte quality.
- Women with a very low LH nadir of <0.5 mIU/mL during their stimulations grew more eggs but had embryos with a lower implantation rate and had lower clinical pregnancy and live birth rates (39, 40). This suggests that very low LH impairs oocyte quality. Some (41, 42) but not all (13, 43, 44) studies observed poorer outcomes with lower serum LH levels, likely due to the short half-life of LH and its pulsatile secretion. However, randomized trials of administering LH activity (typically in the form of hCG or hMG) provides strong support for the beneficial role of adding LH activity to certain patients, such as those with DOR or higher age (reviewed in the following). This also highlights the important clinical distinction between the limited benefit of measuring serum LH levels and the strong benefit of providing additional LH activity during stimulation to certain patients.
- In a fixed-dose IVF randomized trial of recombinant FSH (rFSH) vs. highly purified hMG, women with higher hCG levels on the sixth day of stimulation produced more top-quality embryos (45, 46). Moreover, women randomized to the hMG arm had top-quality embryos with higher implantation and delivery rates (46). This suggests that more LH activity during the midpoint of folliculogenesis improves egg quality.
- Filicori et al. (47) added from 0 to 150 IU of hCG to a fixed-dose of FSH in women in ovulation induction/intrauterine insemination cycles and observed shorter stimulations and less FSH usage when LH activity was present.
- Ovarian stimulations with a fixed-dose of FSH and graded levels of supplemental LH activity (in the form of hCG) show that LH activity shortens time to ovulation and lowers the required dose of FSH, suggesting favorable synergistic action.
- The best US programs include LH activity during their stimulations (48).
- Luteinizing hormone administration in antagonist cycles improved the implantation rates (32).

There is also evidence that LH activity alone is sufficient to support terminal follicle growth. Sullivan et al. (23) and Filicori (49) have both demonstrated that follicles measuring >14 mm will continue to grow when only LH activity is provided. Sullivan et al. (23) studied 24 women in GnRH agonist down-regulated cycles given rFSH until a 14-mm lead follicle was seen. Patients were then randomized to 1 of 4 groups for 2 days: continued rFSH; saline; rLH 150 IU twice a day; and rLH 375 IU twice a day. The E2 levels continued to increase whether FSH or LH was provided but decreased in the saline group. Luteinizing hormone was able to sustain follicular growth despite decreasing FSH levels, implying that follicles measuring ≥14 mm in diameter are responsive to either FSH or LH.

Filicori (50) took this observation further, and a series of studies (51–53) showed that not only is LH activity alone capable of supporting follicle growth but that this LH only support yields the same number of large follicles, the attrition of small follicles, lower P4 levels, and oocytes of higher-quality. His initial case report of a 35-year-old on luteal suppression stimulated with hMG for 7 days and then given only hCG 200 IU daily until trigger on day 13 resulted in nine eggs, 7 of which were mature, five of which fertilized. Three cleavage embryos transferred on day 3 leading to a twin delivery (30). His subsequent studies titrated the FSH dose down and hCG dose up to as much as 200 IU after day 7 of stimulation and observed maintenance of the growth of follicles measuring 14 mm and larger with reduction in the number of small follicles (<14 mm) but also shorter stimulations, less FSH usage, and lower P4 levels at the late follicular phase (reviewed in the study by Filicori et al. (47)). Notably, although an hCG dose of 200 IU is well above the physiological LH equivalent, no negative effect was seen for any of these parameters. No study has found a significant ceiling effect for supplemental LH activity (27).

Who benefits?

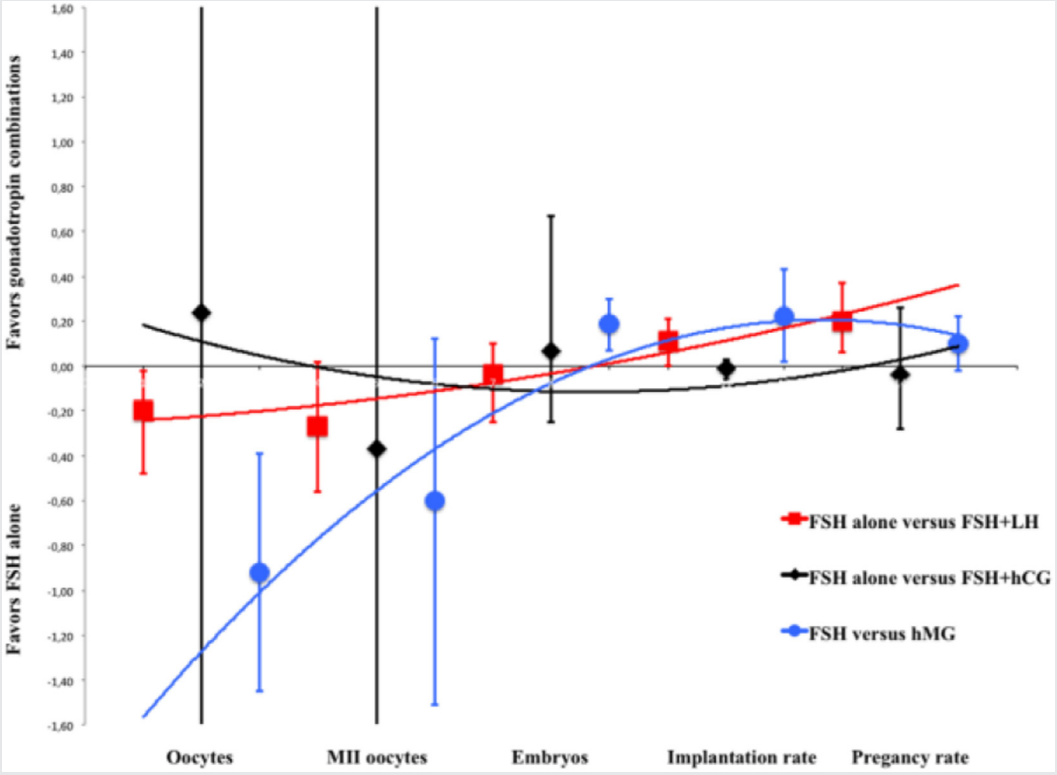
Having documented the need for and benefit of LH activity during mid to late follicular growth on oocyte quality and pregnancy rates, certain questions remain: first, does additional LH activity benefit all women in treatment or only certain subgroups? Second, does the type of LH activity (rLH vs. low-dose hCG vs. hMG) matter in clinical practice? Dozens of randomized controlled trials (RCTs) on these issues have been published, and several systematic reviews and meta-analyses have attempted to address these questions.

A 2017 Cochrane review (35) evaluated adding rLH to rFSH to OSs. Thirty-six RCTs involving 8,125 women were included. The quality of the evidence was very low to moderate. The odds ratio (OR) of live births with rLH + rFSH compared with rFSH alone was 1.32 (32% higher); however, the confidence interval (CI, 0.85–2.06) crossed 1, and thus, this was not statistically significant. However, the OR for the ongoing pregnancy rate was 1.20 (20% higher) but was significantly higher than with rFSH alone (CI, 1.01–1.42). The OHSS OR was 0.38 (62% lower) but with CI (0.14–1.01) just crossing 1. The miscarriage rates were similar (OR, 0.93; CI, 0.62–1.36), the cancellation rates for low response were 23% lower (0.77; CI, 0.54–1.10), and the cancellation rates for imminent OHSS were also lower (by 40%; OR, 0.60; CI, 0.40–0.89). Although some of these comparisons did not achieve statistical significance, everyone favored stimulations that included rLH.

These investigators also reported on some certain subgroup analyses, showing benefit of rLH for the ongoing pregnancy rate in women on GnRH agonist protocols (OR, 1.27; CI, 1.02–1.57) and in women with low response (OR, 2.06; CI, 1.2–3.53). Regarding OHSS, rLH reduced risk in GnRH agonist cycles (OR, 0.16; CI, 0.03–0.88). No statistically significant difference was seen by age.

A different group of investigators also explored which ART subgroups benefit from added LH activity (54–56). They examined six groups: those with a prior poor response to FSH alone; those who were older; those using a GnRH antagonist; those who exhibited a profound LH suppression after GnRH agonist use; those at risk of OHSS; and those with poor ovarian response (by the Bologna criteria). Benefits were seen in three of these groups: prior poor response to FSH monotherapy; those with DOR on antagonist cycles; and women aged 36–39 years. It stands to reason that protocols that increase the risk of profound LH suppression would risk poor oocyte quality and that these protocols should be one focus for LH surveillance or supplementation (Fig. 2) (10).

FIGURE 2



Overall model of meta-analysis results from the study by Santi et al. (10). Note that protocols without luteinizing hormone (LH) activity produced more eggs but fewer embryos with lower implantation and pregnancy rates. FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; hMG = human menopausal gonadotropin; M II oocytes = metaphase 2 oocytes.

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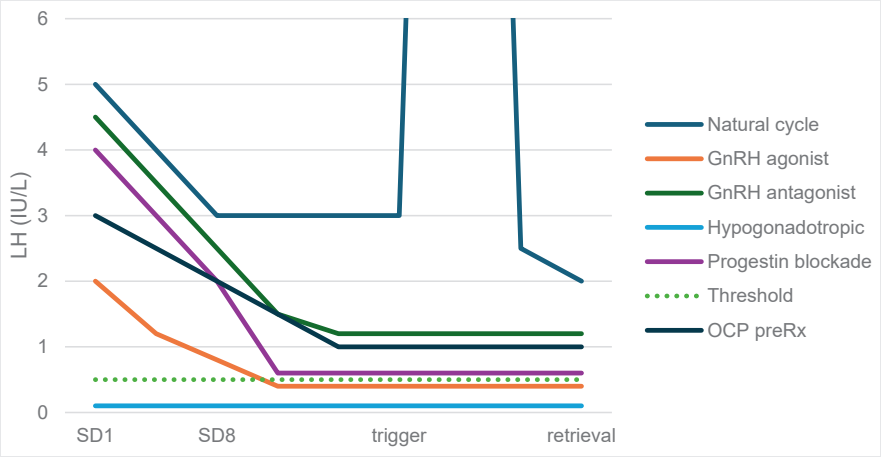
FIGURE 3



Effect of ovarian stimulation protocols on the luteinizing hormone (LH) levels during stimulation. Note that all protocols reduced the LH levels below those seen in natural cycles, with some more than others. Pretreatment with oral contraceptives (OCPs) and gonadotropin-releasing hormone (GnRH) agonists may be particularly suppressive and present throughout the stimulation, whereas GnRH antagonist initiation was most often withheld until midstimulation (72).

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Another ambitious meta-analysis published in 2017 by Santi et al. (10) examined an additional issue, specifically the type of LH activity (hMG, rLH, and hCG). Endpoints were egg number, M2 number, implantation rate, and pregnancy rate. Seventy RCTs were included, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology was employed. Women with PCOS were excluded. Overall, FSH-only stimulations garnered more eggs; however, no more were mature. However, stimulations that included LH activity resulted in more embryos, higher implantation rates, and higher pregnancy rates overall. However, both protocol type (GnRH agonist vs. antagonist) and the type of LH activity mattered.

Regarding the impact of GnRH analogue type, the investigators noted improved outcomes with LH activity in women using GnRH agonist down-regulation for pregnancy. In antagonist cycles, improved outcomes were seen in the implantation rates. They posit that GnRH agonist cycles produce more profound LH suppression, thereby making the benefit of adding LH activity to the stimulation more impactful.

However, more importantly, the type of LH activity (rLH, hMG, or hCG) also had significant impact on clinical outcomes. Specifically, although FSH-only stimulations produced more eggs than any stimulation with added LH activity, rLH stimulations per se produced more pregnancies than did the other types of LH activity. Figures 2 and 3 illustrates the difference in outcomes according to the LH type over sequential steps in the IVF process. Trends suggest that although FSH-only stimulations produce more eggs, as one moves through the IVF process to mature egg number, embryos, implantation rate, and finally pregnancy rate, this difference is reversed, in favor of LH containing stimulations, especially when rLH is employed. To explain why different outcomes may differ depending the particular LH activity provided (rLH, hCG, or hCG containing hMG), they cite in vitro studies showing that despite binding to the same receptor (LHCGR), LH and hCG seem to activate different intracellular pathways (57). In vitro models of granulosa cell response demonstrate that hCG preferentially activates the cAMP production pathway (19), whereas LH preferentially activates ERK1/2 and AKT pathway (58, 59). This may explain these differential in vivo effects. Accordingly, because pregnancy is the goal, the investigators of this meta-analysis argue that it may be advantageous to provide LH activity in the form of rLH or hMG rather than hCG (1, 60, 61).

Taken together, these observations suggest that adding LH activity to FSH in OS for ART reduces the total gonadotropin dose (62), shortens the time to optimal follicle size, lowers late follicular phase P4 production (62), lowers the risk of cancellation, and produces higher-quality embryos (62) and ultimately more births. Furthermore, by mimicking the natural shift to LH dominance in the late luteal phase by reducing FSH but not LH dosing, OHSS risk is reduced because fewer small follicles are recruited into growth.

Despite the robust evidence supporting the use of LH in OS in several categories of patients, there is ongoing debate regarding its universal application. Some studies suggest that younger women with normal ovarian reserve do not benefit significantly from LH supplementation and that its routine use in all OS protocols does not improve clinical outcomes. It may, however, be cost-effective because hMG contains both FSH and LH bioactivity and large follicles respond to both gonadotropins (63). The decision to include LH (rLH) or LH activity (hMG) in OS protocols should, therefore, be individualized, considering patient characteristics such as age, ovarian reserve, and previous responses to stimulation.

Some have worried that although LH is normal and essential for folliculogenesis, perhaps it can be overdone. Is there

evidence of a ceiling, whereby giving too much LH activity reduces pregnancy? Multiple studies suggest no (47, 64–67). Perhaps most convincing is the study by Filicori (68) showing that even with an hCG dose of 200 IU daily (which is equivalent to at least 1,200 IU of LH), no detrimental effects were observed. It seems safe to provide in all cases (50).

Other investigators have examined whether the LH/FSH ratio alters ART outcome (64, 69, 70). One report describe an LH/FSH ratio "sweet spot" for premature P4 elevation and found the fewest early P4 elevations with ratios between 0.3 and 0.8, suggesting a minor effect for those doses with the most LH activity (27). However, rather than focusing on the ratio, it seems more appropriate to focus on ensuring that a sufficient LH action is in place to undergird normal folliculogenesis and oocyte quality.

KEY POINTS

- Luteinizing hormone and FSH act synergistically to produce ovarian steroids and healthy oocytes.
- Some IVF cycles are LH-deficient due to patient characteristics or protocol choices. These include patients with hypogonadotropism or who are oversuppressed because of GnRH analogues or oral contraceptives. Progestin protocols may also risk oversuppression. Protocols containing some form of LH activity can mitigate these risks.
- There is also evidence that women with DOR unexpected poor response or higher age have better outcomes in cycles with LH activity.
- Although both LH and hCG bind to the same receptor, they activate different intracellular signaling pathways and seem to have somewhat distinct clinical effects.

PRACTICE IMPLICATIONS

Ensure sufficient LH tone

Evidence is strong that in LH-deficient cycles, oocyte and embryo quality are reduced. The risk of LH deficiency is elevated in those with hypothalamic hypogonadism, GnRH agonist suppression, and prolonged pretreatment with oral contraception. These groups benefit from protocols that contain LH activity in some form. The effect of "progestin priming" (a misnomer) on follicular LH secretion is currently uncertain but may increase the risk of low LH levels during stimulation. In the context of DOR, adding LH reduces the risk of cycle cancellation, likely due to its synergistic action with LH on later follicular growth.

In cases where low follicular LH tone is a risk, one can either check the midfollicular LH (or hCG) level and supplement if low or automatically add it to the protocol. The latter seems to be safe because there is no obvious ceiling effect.

Reducing the need for freeze-all

In cycles with an increase in the P4 level above 1.5 ng/mL before trigger, the pregnancy rates are reduced (71). Because sufficient LH reduces the chance for such a premature P4 elevation, the opportunity for a fresh transfer is increased.

Reducing OHSS risk

Because LH can sustain the growth of large follicles without the need for concurrent FSH, in cases where OHSS is a concern, once an adequate cohort has been developed, one can withhold further FSH and provide only LH activity to prevent the recruitment of new cohorts of smaller follicles that would increase the risk of OHSS without garnering more mature eggs.

Reducing medication cost?

Currently, the price of gonadotropin medications is largely tied to the amount of FSH it contains. Human menopausal gonadotropin products contain an equal amount of LH and FSH activity; however, there is no extra charge for the LH component. Nonetheless, as reviewed earlier, large follicles respond equally well to FSH and LH. This means that 75 IU of an hMG product will provide the same degree of stimulation to large follicles as 150 IU of rFSH at a 50% lower cost.

FUTURE DIRECTIONS

As research into the role of LH in OS continues, future studies should focus on identifying biomarkers that can predict which patients are most likely to benefit from LH supplementation and, notably, markers of oocyte quality. Additionally, more refined protocols that optimize the timing and dosage of LH could further improve outcomes for women undergoing ART. The integration of molecular biology with clinical practice will likely lead to more personalized and effective treatment strategies in the future.

CONCLUSION

The inclusion of LH in contemporary OS protocols is supported by a growing body of molecular and clinical evidence. The unique role of LH in follicle maturation, ovulation, and luteinization, as well as its distinct effects compared with hCG, make it an essential factor in optimal ART outcomes. To date, evidence supports providing LH during OS to women with hypothalamic amenorrhea, diminished ovarian response, prior poor response to FSH-only stimulations, and a low midfollicular LH level. It also reduces OHSS risk by supporting terminal follicle growth without recruiting new follicles into growth. Because there is limited evidence of a ceiling effect, LH can be added to all OS protocols for convenience. However, as our understanding of the difference between LH and hCG action improves, their role in optimal ART protocols is likely to become more refined.

CRediT Authorship Contribution Statement

James P. Toner: Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Paul Pirtea:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization.

Declaration of Interests

J.P.T. has nothing to disclose. P.P. has nothing to disclose.

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