

REVIEW

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The role of recombinant LH in ovarian stimulation: what's new?

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Abstract

It is widely recognized that luteinizing hormone (LH) activity is pivotal during folliculogenesis. Nonetheless, the use of LH during ovarian stimulation remains a matter of debate. Indeed, women with good LH function are able to sustain follicle growth and maturation during ovarian stimulation carried out with regimens based on follicle-stimulating hormone (FSH) alone. However, evidence exists that LH activity could be necessary in specific infertile subgroups undergoing assisted reproduction treatment (ART) who are characterized by a functional or constitutive LH deficiency. For instance, women with reduced sensitivity to gonadotropins, also called hypo-responders, usually present with a genetic condition that could impair the function of LH. Furthermore, women of advanced reproductive age present a less functional LH system and consequently reduced androgen production. Reduced ovarian sensitivity and advanced reproductive age represent the main criteria proposed by the POSEIDON group to identify women with impaired prognosis when undergoing ART. Hypogonadotropic hypogonadal women are characterized by undetectable LH levels, thus the addition of LH activity during stimulation is mandatory to achieve satisfactory follicular recruitment. The aim of the present review is to describe the role of recombinant LH in ovarian stimulation, identifying the specific infertile population for whom LH supplementation could improve the outcome of ART.

Keywords Luteinizing hormone, Ovarian stimulation, IVF, ART, POSEIDON, Poor responders, Hypo-responders

Introduction

Luteinizing hormone (LH) plays a crucial role in folliculogenesis. According to the 'two cell – two gonadotropin' model [1, 2], LH exerts its activity in theca cells, inducing androgen synthesis, while follicle-stimulating hormone (FSH) induces expression of the aromatase enzyme which, in turn, converts androgens into estrogens. This view has been reconsidered in light of evidence supporting the effect of LH beyond theca cells [3–5]. It was widely recognized that, in granulosa cells, FSH and estrogens induce the expression of LH choriogonadotropin receptor (LHCGR) from the early/mid-follicular phase [1, 6, 7]. During this stage, LH could mimic the actions of FSH on granulosa cells, including the induction of aromatase activity [8, 9]. From a clinical point of view, LH

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activity could sustain alone follicular growth in the last stage of ovarian stimulation (OS) in women undergoing assisted reproduction independently of FSH [10]. In detail, Filicori et al. observed that women who received only LH in the form of low-dose human chorionic gonadotropin (hCG) in the last part of OS had similar estradiol levels and number of large (> 14 mm) preovulatory follicles than those who received only FSH throughout the stimulation [10]. Furthermore, stimulation with LH alone could significantly reduce the numbers of small antral follicles, thus facilitating selection of large follicles [10]. This study therefore supports the concept that the growth of dominant and larger follicles depends mainly on the activity of a functional LHCGR [7]. The most recent formulations are based on pure LH, which is characterized by more pronounced anti-apoptotic and proliferative effects than hCG [11, 12]. LH could also prevent the apoptosis induced by the cytotoxic effect of chemotherapeutic agents, thereby preserving fertility in *in vivo* models [13].

In synergy with FSH, LH could promote the production of paracrine factors playing a crucial role in folliculogenesis, such as insulin-like growth factors and inhibin B [5, 14]. LH is also fundamental to ovulation, since it induces protease activity and oocyte maturation [15]. Finally, LH is the main inducer of luteinization, essential for progesterone production and endometrial support during implantation [15].

Recent studies have suggested that LH might have extragonadal actions, as the LHCGR is expressed in the human endometrium [16, 17] and in non-gonadal tissue [18]. However, the relevance of LHCGR in non-gonadal tissue [18–20] is still debated. Although exciting results were obtained in mice [21–23], the existence of human extragonadal gonadotropin receptors would imply an absence of off-target endocrine effects; much of these data should be revised in light of lack of specificity of the detection methods available, artificial experimental settings, and methodological biases [24–29].

The use of LH during OS has been a matter of debate for several years, supported by the fact that medications used to prevent premature ovulation, such as gonadotropin-releasing hormone (GnRH) antagonists and agonists, will cause a transient deficiency of endogenous LH [30–32]. Among women in whom LHCGR-dependent signals are sufficient to support folliculogenesis, the need for LH supplementation appears to be limited during OS [31]. In fact, residual circulating LH, likely to persist during suppression of the pituitary, may be sufficient to sustain LHCGR activity and support follicle growth and maturation during treatment with FSH alone. This effect is observable during routine *in vitro* fertilization treatment in the general population, who do not require

LH supplementation during OS to obtain a successful response to OS [33, 34]. Nonetheless, there is evidence that LH activity could be necessary in specific infertile subgroups undergoing IVF treatment.

The aim of the present review is to describe the role of recombinant LH supplementation during OS, identifying the specific infertile population for whom LH activity supplementation could improve the outcomes of assisted reproduction treatment (ART).

Methods

This narrative review was conducted through a literature search in PubMed, Scopus, Embase, and the ISI Web of Science database. The following search terms were used: 'LH', 'recombinant LH', 'luteinizing hormone', 'ovarian stimulation', 'ART', 'IVF', 'ovarian stimulation', and 'ovulation induction'. We mainly included clinical studies that analyzed the impact of LH on controlled OS, dating from the inception of the database used to June 2023 (Table 1). No language restriction was adopted.

Results and discussion

LH in women with poor ovarian response to stimulation according to the ESHRE/Bologna criteria

The ESHRE/Bologna criteria are widely adopted to identify women with poor response to OS [35]. These criteria are based on the presence of at least two of the following characteristics: (i) advanced maternal age (> 40 years) or any other poor ovarian response risk factor; or (ii) a previous episode of poor ovarian response (POR; defined as ≤ 3 oocytes retrieved after a conventional stimulation dose), a low ovarian reserve test in terms of anti-Müllerian hormone (AMH), and a low antral follicle count (AFC). These criteria have been debated, because they risk classifying a very heterogeneous group of women with a different reproductive prognosis following IVF treatment [36–39]. Indeed, in a large retrospective study ($N=821$ women), live birth rates were significantly different in various subgroups of poor ovarian responders fulfilling the Bologna criteria, with the most favorable outcome in younger women (ages < 40 years) [40]. Similarly, Romito et al. (2020) observed that the cumulative live birth rate was statistically significantly different among subgroups of poor ovarian responders classified by the Bologna criteria [41]. So far, the largest multicenter randomized controlled trial (RCT) to explore the use of recombinant human LH (r-hLH) in poor ovarian responders aligned with the Bologna criteria was conducted by Humaidan et al. (2017) [42]. A total of 939 women undergoing IVF treatment were randomized to receive OS with recombinant human FSH (r-hFSH) and r-hLH (300 and 150 IU, respectively) from day 1 of stimulation or r-hFSH alone (300 IU daily). All women

Table 1 Key clinical articles included in the review

	Study design	Patients involved	Intervention	Comparator	Results
Hypo-responders					
Conforti et al. 2019	Meta-analysis (4 RCTs + 1 prospective study)	Hypo-responders	r-hFSH and r-hLH co-treatment	r-hFSH monotherapy	Significantly higher clinical pregnancy rates, implantation rates, number of oocytes retrieved
Advanced maternal age					
Conforti et al. 2021	Meta-analysis (12 RCTs)	Advanced maternal age (≥ 35 years)	r-hFSH and r-hLH co-treatment	r-hFSH monotherapy	Significantly higher clinical pregnancy rates, and implantation rates, in women between 35–40 years old
Hypogonadotropic hypogonadal					
Carone et al. 2012 [94]	RCT	Hypogonadotropic hypogonadal women	r-hFSH and r-hLH co-treatment	hMG	Significantly higher clinical pregnancy rate
Huseyin et al. 2019 [99]	Retrospective study	Hypogonadotropic hypogonadal women	r-hFSH and r-hLH co-treatment	hMG	Significantly lower cancellation rate
Progesterone rise					
Werner et al. 2014 [87]	Retrospective study	10,280 patients first IVF cycle	FSH plus LH formulations	FSH monotherapy	Stimulations using no administered LH had the highest risk of progesterone elevation ≥ 1.5 ng/mL
Hugues et al. 2012 [91]	Systematic review (34 studies)	Women undergoing MAR techniques	hMG, r-hLH, or hCG	FSH monotherapy	Comparable risk of progesterone rise
Implantation failure					
Rahman et al. 2017 [92]	RCT	Women with 2 previous failed implantations	r-hFSH and r-hLH co-treatment	r-hFSH monotherapy	Significantly higher implantation rate and pregnancy rate; significantly lower abortion rate
Poor response according to Bologna criteria					
Humaidan et al. 2017 [42]	RCT	Women fulfilling Bologna criteria	r-hFSH and r-hLH co-treatment	r-hFSH monotherapy	Significantly higher cumulative live birth rate in women with moderate or severe BSC
Lehert et al. 2021 [44]	Retrospective study	Women fulfilling Bologna criteria	r-hFSH and r-hLH co-treatment	r-hFSH monotherapy	Significantly higher cumulative live birth rate in women with moderate or severe BSC

BSC baseline severity score, FSH follicle-stimulating hormone, hCG human chorionic gonadotropin, hMG human menopausal gonadotropin, LH luteinizing hormone, MAR medically assisted reproduction, RCT randomized controlled trial, r-hFSH recombinant human FSH, r-hLH recombinant human LH

underwent a long GnRH agonist down-regulation protocol.

In the total population, no differences were observed between the two groups of treated patients regarding implantation rate or live birth rate. However, a post-hoc analysis revealed that r-hFSH and r-hLH co-treatment actually had a positive effect on the live birth rate of specific subgroups of women fulfilling the Bologna criteria. Thus, the study population was stratified into three different groups, adopting a so-called Baseline Severity Score (BSC). This score was based on the following characteristics: (i) age ≥ 40 ; (ii) reduced ovarian reserve (AMH < 0.5 ng/mL) or < 2 oocytes retrieved during the

most recent ART cycle. The BSC for a subject could reach the value of 0 (mild) if none of these criteria were met; 1 (moderate) if one criterion was met; or 2 (severe) if two criteria were met. Interestingly, women with moderate or severe BSC had a higher live birth rate when supplemented with r-hLH compared to patients treated with r-hFSH alone. Conversely, women with a mild BSC had a higher live birth rate when stimulated with r-hFSH alone, compared to patients supplemented with r-hLH. Subsequently, the BSC score was ‘renamed’ as the Poor Responder Outcome Prediction (PROsPeR) score, which showed good discrimination to predict the live birth rate of women fulfilling the Bologna criteria [43, 44]. Recently,

in a large retrospective real-world analysis of 9,787 IVF treatments, Leheret et al. (2021) confirmed that the cumulative live birth rate (defined as the occurrence of live birth per started controlled OS further to transfer of fresh and frozen embryos generated from the same OS) was significantly higher in patients with a moderate or severe PROsPeR score who received r-hFSH and r-hLH co-treatment, compared with moderate or severe PROsPeR score patients who received r-hFSH monotherapy [45].

In conclusion, r-hLH supplementation could improve the live birth and cumulative live birth rates in specific subgroups of women fulfilling the Bologna criteria. In detail, women with the highest PROsPeR score are likely to benefit most from r-hLH supplementation during OS.

LH in hypo-responders (POSEIDON groups 1 and 2)

The hypo-responsive patient is characterized by a reduced sensitivity to exogenous gonadotropins during IVF treatment [46], displaying a discrepancy between the AFC at the beginning of stimulation and the number of preovulatory follicles and oocytes retrieved after stimulation [46]. These patients often have a stagnation in follicular growth during OS, especially when undergoing a long GnRH protocol or a few days after the introduction of the GnRH antagonist [47, 48]. Compared with normal responders, hypo-responders have a lower chance of ART success, and were therefore included in the POSEIDON criteria. Indeed, POSEIDON groups 1 and 2 show a reduced ovarian response to OS, with a suboptimal (4–9 oocytes) or poor (≤ 3 oocytes) retrieval of oocytes despite an adequate ovarian reserve ($\text{AMH} > 1.2 \text{ ng/mL}$ or $\text{AFC} > 5$) [39, 49, 50].

So far, three RCTs and one prospective cohort study have investigated the effect of LH supplementation in women with a hypo-response profile [12, 47, 48, 51]. All women included in these studies underwent a long GnRH agonist down-regulation protocol and experienced follicular stagnation during OS. A recent meta-analysis performed on those studies concluded that the addition of r-hLH during OS lead to a significant increase in oocyte number, implantation rate, and clinical pregnancy rate [52]. Only the RCT conducted by Ferraretti et al. (2004) reported data about live birth rate per cycle, confirming an increased live birth rate in hypo-responders undergoing stimulation with r-hFSH and r-hLH co-treatment compared with those who received r-hFSH alone during their OS [47]. Notably, these researchers also observed a significantly higher pregnancy rate in hypo-responders who underwent r-hFSH and r-hLH co-treatment compared to those who received combination therapy with r-hFSH and human menopausal gonadotropin (hMG).

The reason behind the need to add LH activity in women affected by hypo-responsiveness is still not fully clear, but it has been hypothesized that women with hypo-response have a relative LH deficiency [31]. In other words, in the hypo-responder patient, endogenous LH levels are insufficient to secure appropriate stimulation when the pituitary axis is suppressed [32]. The LH relative deficiency that characterizes women with hypo-response could be linked to specific genetic variants, affecting the LH system. Indeed, GnRH agonist down-regulated women who had a specific genetic variant of the LH β chain showed a typical hypo-response profile during OS with exogenous FSH and required higher consumption of FSH during OS [53, 54]. More recently, Ku et al. (2021) observed that the variant LH β gene was associated with a lower clinical pregnancy rate in GnRH antagonist cycles, but not in long GnRH agonist down-regulated cycles [55]. This observation is consistent with several lines of evidence suggesting that endogenous LH levels are more suppressed during GnRH antagonist treatment compared with the GnRH agonist down-regulated cycle [56–58].

Finally, women who express a common variant of the LHCGR receptor also seem to benefit from exogenous LH during OS [59, 60]. Hypo-response to monotherapy with FSH might be linked to the paracrine activity exerted by exogenous LH in women with hypo-response. In detail, r-hLH supplementation in women with hypo-response could modify the follicular fluid steroid composition, changing it to a more physiologic composition in terms of estrogens and progestins [61, 62]. This finding emerges from a prospective analysis of 111 follicular fluid samples obtained from women with hypo-response who underwent r-hFSH/r-hLH co-treatment versus r-hFSH monotherapy [62].

The appropriate dosage and timing of r-hLH in women with hypo-response is still a matter of debate. In women undergoing the long GnRH agonist down-regulation protocol, it seems that r-hLH should be supplemented once follicular stagnation is observed, typically between days 7 and 10 of OS (estradiol levels $< 180 \text{ pg/mL}$, no follicles $> 10 \text{ mm}$ diameter) [47, 48]. Regarding the dosage, hypo-responders supplemented with 150 IU of r-hLH daily ('rescue protocol') had a significantly higher number of oocytes and mature oocytes retrieved compared to hypo-responders who received 75 IU r-LH daily. So far, very few studies and no RCTs have investigated the effect of r-hLH supplementation in women with hypo-response who were co-treated with a GnRH antagonist; however, the follicular stagnation pattern is the same and is usually seen 2–3 days after starting GnRH antagonist co-treatment.

In conclusion, women with hypo-response seem to benefit from r-hLH supplementation during OS; the most appropriate dosage and timing in women undergoing a long GnRH agonist down-regulation regimen seems to be 150 IU/day r-LH, starting from the day that follicular stagnation is detected.

LH in women of advanced reproductive age (POSEIDON groups 2 and 4)

Advanced reproductive age is characterized by a reduced reproductive prognosis in ART [39, 63]. A more pronounced decline is observed after 35 years of age, reflecting a gradual decrease in ovarian reserve and oocyte quality [64, 65]. Indeed, the IVF success rate decreases dramatically, to <5%, beyond the age of 43/44 years [63]. Chronological age is generally considered one of the main parameters to predict the prognosis of ART. In contrast to the Bologna criteria, the POSEIDON group suggested 35 years as the most appropriate cut-off and identified four different segments of prognosis based on age. Advanced-age women with a good ovarian reserve were stratified into POSEIDON group 2, whereas those with a poor ovarian reserve were stratified into POSEIDON group 4, with a distinct significant difference in reproductive outcomes between groups [38, 66, 67].

Aneuploidy rates of human embryos are probably the most relevant cause of the decrease in IVF success rate in advanced-age women [68]. In a recent study, it was demonstrated that the probability of having a euploid embryo decreases from 24.5 to 1.2% in women aged 28–44 years [69]. Apart from embryo quality, several lines of research have suggested that advanced reproductive age is also associated with relative LH deficiency [31, 70]. This hypothesis is supported by the fact that LH-related androgen production dramatically decreases in advanced age women [71–73]. Although it has been hypothesized that the androgen deficiency seen in the aging woman could be compensated by androgen supplementation [74], some researchers have suggested that exogenous LH supplementation would more optimally induce local follicular androgen production compared to exogenous androgen supplementation [75, 76].

From a clinical point of view, several RCTs have been reported comparing r-hFSH and r-hLH co-treatment versus r-hFSH monotherapy in women of advanced age [77–79]. A recent meta-analysis of RCTs concluded that r-hFSH/r-hLH co-treatment during OS significantly benefited women between the age of 35 and 40 years, in terms of implantation (OR 1.49, CI 95% 1.10–2.01; $p=0.01$) and clinical pregnancy rate (OR 1.45, CI 95% 1.05–2.00; $p=0.03$), whereas no difference was seen in higher-age groups [80]. The lack of effect beyond 40 years

of age could be masked by the impact of age-related aneuploidy rates on IVF prognosis [68, 80].

The most plausible positive effect exerted by exogenous LH supplementation seems to be related to an improvement in oocyte/embryo quality [81]. Thus, the follicular fluid LH level was identified as a good marker of oocyte/embryo competence [82]. In a large age-adjusted RCT, Bosch et al. (2011) observed higher fertilization rates in women aged 35–39 years co-treated with r-hFSH and r-hLH versus r-hFSH monotherapy ($68\% \pm 25\%$ vs. $61.2\% \pm 27.3\%$; $p=0.027$) [78]. In another study, Ruvolo et al. (2007) observed that in women treated with exogenous r-hLH, the apoptosis rate in cumulus cells, expressed as lower rate of chromatin fragmentation (12.1% vs. 18.2%; $p<0.05$), and number of immature oocytes (0.58 vs. 2.33; $p<0.01$) were significantly reduced compared to women treated with r-hFSH alone [12].

In conclusion, LH activity could be proposed in advanced-age women undergoing OS; however, a significant effect in terms of implantation and clinical pregnancy was only seen in women between 35 and 40 years of age.

LH in women with progesterone rise and impaired embryo implantation

Apart from a positive effect on oocyte/embryo quality, the improved effect of LH supplementation on implantation might also be explained by an LH-mediated effect on the endometrium [83]. Thus, LH is able to modulate several factors that play a role during embryo implantation, such as colony-stimulating factor-1, cytokine leukemia inhibiting factor, glycodelin, interleukin-1, integrins, and mucin 1 [84].

Another possible benefit exerted by LH activity during OS is the potential reduction in late follicular serum progesterone levels, which by retrospective analyses has been suggested to be associated with lower ongoing implantation and pregnancy rates in fresh embryo transfer IVF cycles [85, 86]. Thus, in an analysis of 10,280 patients undergoing their first IVF cycle, OS without LH activity (hMG) resulted in a significantly higher risk of late follicular progesterone rise [87]. In the same line, the MERIT trials randomly assigned women to receive either r-hFSH or hMG alone showed significantly higher late follicular progesterone levels in patients treated with r-hFSH compared to those receiving hMG-only protocols [88]. This finding could be explained by the fact that progesterone rise is mainly driven by high FSH dosing during OS [89]. Conversely, by suppressing the development of small follicles, LH activity could reduce progesterone levels [85, 90]. However, a systematic review of 34 studies did not confirm that LH activity could have a modulating effect on serum progesterone levels [91]. Indeed, the

authors observed a decrease in serum progesterone only when LH was prescribed from the beginning of OS; this makes sense from a physiological point of view, as this is the time point to suppress the growth of smaller follicles [91].

To date, only one study has explored the effect of exogenous LH supplementation in women with a history of implantation failure [92]. In that study, 61 women with a history of two failed embryo transfers who underwent OS, co-treated with a flexible GnRH antagonist protocol, were randomized into two groups: the study group, which was supplemented with r-hLH from the day of GnRH antagonist co-administration ($n=29$); and the control group ($n=32$), which was stimulated with r-hFSH alone. Interestingly, the implantation (19% vs. 9%; $p<0.01$) and positive pregnancy test (48.3% vs. 25%; $p<0.03$) were significantly higher in the study group versus control group; moreover, the pregnancy loss rate was significantly lower in the study group versus control group (21% vs. 37.5%; $p<0.01$).

Despite these promising findings, the evidence collected so far is not sufficient to recommend the use of r-hLH in women with a history of implantation failure. As for late follicular progesterone rises and r-hLH supplementation, conflicting evidence exists; but the effect of LH activity appears to be more pronounced when LH is administered from day 1 of OS.

LH in hypogonadotropic hypogonadal women

In women with hypogonadotropic hypogonadism (HH) with very low gonadotropin levels (World Health Organization group I anovulatory women), the accumulated evidence so far supports the need for LH activity during

OS [93, 94]. Indeed, r-hFSH stimulation alone cannot support follicular growth in women with HH [93, 95, 96]. In other words, HH women do not have sufficient circulating endogenous LH levels to support optimal follicular development. Both human menopausal gonadotropin (hMG) and r-FSH with r-hLH, compared to r-hFSH alone, resulted in a significantly higher ovarian response to OS in HH women [97, 98]. In a single RCT, 35 women with HH were randomized to receive 150 IU of highly purified hMG ($n=18$) or 150 IU r-hFSH plus 75 IU r-hLH daily for a maximum of 16 days ($n=17$) [94]. Women stimulated with r-hLH had significantly higher pregnancy rates compared with those who underwent hMG stimulation (55.6% vs. 23.3%; $p=0.01$) [94]. Nonetheless, ovulation induction was similar between groups.

In a more recent retrospective analysis involving a total of 99 HH women undergoing OS and intrauterine insemination, similar pregnancy rates were observed comparing women treated with r-hFSH and r-hLH versus those who received hMG for OS. Nonetheless, the cancellation rates were significantly higher in women who underwent hMG stimulation versus those co-treated with r-hLH (29% vs. 8.1%; $p<0.05$) [99]. Taken together, despite being more costly, r-hLH supplementation in the HH woman seems to result in a better reproductive outcome compared to hMG.

Knowledge gaps and future research

The evidence so far collected suggests that LH supplementation could be considered in specific IVF women. Nonetheless, further analysis is required in larger populations with specific prognostic classifications based on POSEIDON criteria. Furthermore, few studies have

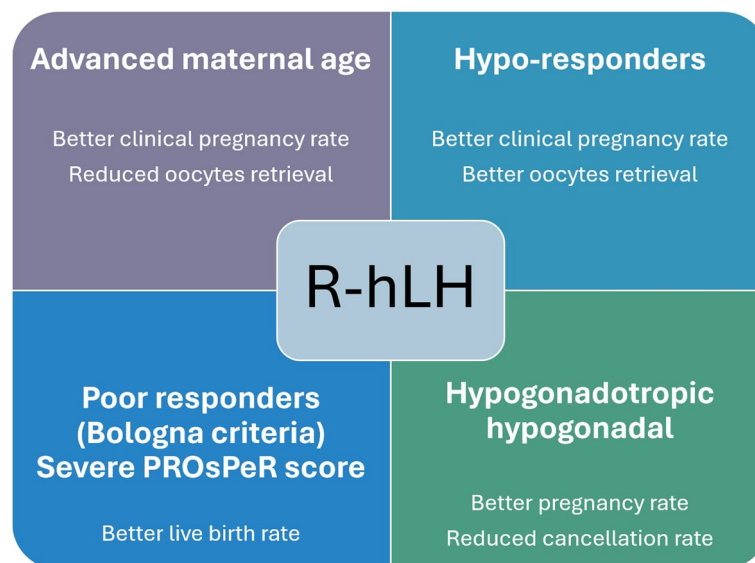


Fig. 1 Main patient populations benefiting from LH supplementation, and the key mechanisms involved

investigated the effect of LH in hypo-responder women undergoing antagonist protocols. Another interesting field for future research is the growing role of r-hLH in promoting AFC recruitment [100] and fertility preservation [13]; despite promising findings, more study data are required before any clinical conclusions can be drawn.

Conclusion

In conclusion, this literature search on the effect of r-hLH in specific - and LH activity (HMG) in general - supports the use of r-hLH for OS in the following sub-groups of IVF patients: (i) the POR patient aligned with the Bologna POR criteria with the highest PROsPeR score; (ii) the hypo-responder to r-hFSH monotherapy (POSEIDON groups 1 and 2); (iii) patients of advanced reproductive age up to and including 40 years of age (POSEIDON groups 2 and 4); and (iv) the hypogonadotropic hypogonadal patient (Fig. 1). For all subgroups to obtain the most optimal benefit, r-hLH supplementation should commence from day 1 of ovarian stimulation. Whether further patient populations might benefit from supplementation with r-hLH needs to be explored in future trials and analyses.

Abbreviations

AFC	antral follicle count
AMH	anti-Müllerian hormone
ART	assisted reproduction treatment
BSC	Baseline Severity Score
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
HH	hypogonadotropic hypogonadism
hMG	human menopausal gonadotropin
LH	luteinizing hormone
LHCGR	luteinizing hormone choriogonadotropin receptor
OS	ovarian stimulation
POR	poor ovarian response
RCT	randomized controlled trial

Authors' contributions

All authors (CA, LV, FC, AC, and PH) were involved in the drafting, review, and final approval of the manuscript for publication.

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References

- Hillier SG, Whitelaw PF, Smyth CD. Follicular oestrogen synthesis: the two-cell, two-gonadotrophin model revisited. *Mol Cell Endocrinol*. 1994;100:51–4.
- Ryan KJ. Granulosa-thecal cell interaction in ovarian steroidogenesis. *J Steroid Biochem*. 1979;11:799–800.
- Alviggi C, Mollo A, Clarizia R, De Placido G. Exploiting LH in ovarian stimulation. *Reprod Biomed Online*. 2006;12:221–33.
- Palermo R. Differential actions of FSH and LH during folliculogenesis. *Reprod Biomed Online*. 2007;15:326–37.
- Alviggi C, Clarizia R, Mollo A, Ranieri A, De Placido G. Who needs LH in ovarian stimulation? *Reprod Biomed Online*. 2011;22:s33–41.
- Jeppesen JV, Kristensen SG, Nielsen ME, Humaidan P, Dal Canto M, Fadini R, et al. LH-receptor gene expression in human granulosa and cumulus cells from antral and preovulatory follicles. *J Clin Endocrinol Metab*. 2012;97:E1524–31.
- Filicori M, Cognigni GE, Pocognoli P, Ciampaglia W, Bernardi S. Current concepts and novel applications of LH activity in ovarian stimulation. *Trends Endocrinol Metab*. 2003;14:267–73.
- Casarini L, Santi D, Simoni M, Poti F. Spare luteinizing hormone receptors: facts and fiction. *Trends Endocrinol Metab*. 2018;29:208–17.
- Sullivan MW, Stewart-Akers A, Krasnow JS, Berga SL, Zeleznik AJ. Ovarian responses in women to recombinant follicle-stimulating hormone and luteinizing hormone (LH): a role for LH in the final stages of follicular maturation. *J Clin Endocrinol Metab*. 1999;84:228–32.
- Filicori M, Cognigni GE, Tabarelli C, Pocognoli P, Taraborrelli S, Spetoli D, et al. Stimulation and growth of antral ovarian follicles by selective LH activity administration in women. *J Clin Endocrinol Metab*. 2002;87:1156–61.
- Casarini L, Riccetti L, De Pascali F, Nicoli A, Tagliavini S, Trenti T, et al. Follicle-stimulating hormone potentiates the steroidogenic activity of chorionic gonadotropin and the anti-apoptotic activity of luteinizing hormone in human granulosa-lutein cells in vitro. *Mol Cell Endocrinol*. 2016;422:103–14.
- Ruvolo G, Bosco L, Pane A, Morici G, Cittadini E, Roccheri MC. Lower apoptosis rate in human cumulus cells after administration of recombinant luteinizing hormone to women undergoing ovarian stimulation for in vitro fertilization procedures. *Fertil Steril*. 2007;87:542–6.
- Rossi V, Lispi M, Longobardi S, Mattei M, Di Rella F, Salustri A, et al. LH prevents cisplatin-induced apoptosis in oocytes and preserves female fertility in mouse. *Cell Death Differ*. 2017;24:72–82.
- Huang ZH, Clayton PE, Brady G, Morris ID. Insulin-like growth factor-I gene expression in human granulosa-lutein cells. *J Mol Endocrinol*. 1994;12:283–91.
- Munoz E, Bosch E, Fernandez I, Portela S, Ortiz G, Remohi J, et al. The role of LH in ovarian stimulation. *Curr Pharm Biotechnol*. 2012;13:409–16.
- Sacchi S, Sena P, Degli Esposti C, Lui J, La Marca A. Evidence for expression and functionality of FSH and LH/hCG receptors in human endometrium. *J Assist Reprod Genet*. 2018;35:1703–12.
- Gridelet V, Tsampalas M, Berndt S, Hagelstein M-T, Charlet-Renard C, Conrath V, et al. Evidence for cross-talk between the LH receptor and LH during implantation in mice. *Reprod Fertil Dev*. 2013;25:511–22.
- Pakarainen T, Ahtiainen P, Zhang F-P, Rulli S, Poutanen M, Huhtaniemi I. Extragonadal LH/hCG action—not yet time to rewrite textbooks. *Mol Cell Endocrinol*. 2007;269:9–16.

19. Ziecik AJ, Derecka-Reszka K, Rzucidło SJ. Extragonadal gonadotropin receptors, their distribution and function. *J Physiol Pharmacol*. 1992;43:33–49.
20. Ziecik AJ, Kaczmarek MM, Blitek A, Kowalczyk AE, Li X, Rahman NA. Novel biological and possible applicable roles of LH/hCG receptor. *Mol Cell Endocrinol*. 2007;269:51–60.
21. Xiong J, Kang SS, Wang Z, Liu X, Kuo T-C, Korkmaz F, et al. FSH blockade improves cognition in mice with Alzheimer's disease. *Nature*. 2022;603:470–6.
22. Liu P, Ji Y, Yuen T, Rendina-Ruedy E, DeMambro VE, Dhawan S, et al. Blocking FSH induces thermogenic adipose tissue and reduces body fat. *Nature*. 2017;546:107–12.
23. Sun L, Peng Y, Sharrow AC, Iqbal J, Zhang Z, Papachristou DJ, et al. FSH directly regulates bone mass. *Cell*. 2006;125:247–60.
24. Rivero-Müller A, Huhtaniemi I. Genetic variants of gonadotrophins and their receptors: impact on the diagnosis and management of the infertile patient. *Best Pract Res Clin Endocrinol Metab*. 2022;36:101596.
25. Chrusciel M, Ponikwicka-Tyszkó D, Wolczynski S, Huhtaniemi I, Rahman NA. Extragonadal FSHR expression and function-Is it real? *Front Endocrinol (Lausanne)*. 2019;10:32.
26. Casarini L, Simoni M. Recent advances in understanding gonadotropin signaling. *Fac Rev*. 2021;10:41.
27. Mann ON, Kong C-S, Lucas ES, Brosens JJ, Hanyaloglu AC, Brighton PJ. Expression and function of the luteinizing hormone chorionadotropin receptor in human endometrial stromal cells. *Sci Rep*. 2022;12:8624.
28. Stelmaszewska J, Chrusciel M, Doroszko M, Akerfelt M, Ponikwicka-Tyszkó D, Nees M, et al. Revisiting the expression and function of follicle-stimulation hormone receptor in human umbilical vein endothelial cells. *Sci Rep*. 2016;6:37095.
29. Elenkov A, Wirestrand E, Hagsund A, Huhtaniemi I, Giwercman YL, Giwercman A. Non-reproductive effects of follicle-stimulating hormone in young men. *Andrology*. 2023;11:471–7.
30. Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. *Hum Reprod Update*. 2017;23:560–79.
31. Bosch E, Alviggi C, Lisi P, Conforti A, Hanyaloglu AC, Chuderland D, et al. Reduced FSH and LH action: implications for medically assisted reproduction. *Hum Reprod*. 2021;36:1469–80.
32. Westergaard LG, Laursen SB, Andersen CY. Increased risk of early pregnancy loss by profound suppression of luteinizing hormone during ovarian stimulation in normogonadotrophic women undergoing assisted reproduction. *Hum Reprod*. 2000;15:1003–8.
33. Alviggi C, Conforti A, Esteves SC, Andersen CY, Bosch E, Bühler K, et al. Recombinant luteinizing hormone supplementation in assisted reproductive technology: a systematic review. *Fertil Steril*. 2018;109:644–64.
34. Griesinger G, Shapiro DB. Luteinizing hormone add-back: is it needed in controlled ovarian stimulation, and if so, when? *J Reprod Med*. 2011;56:279–300.
35. Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, Gianaroli L, et al. ESHRE consensus on the definition of poor response to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod*. 2011;26:1616–24.
36. Papathanasiou A. Implementing the ESHRE poor responder criteria in research studies: methodological implications. *Hum Reprod*. 2014;29:1835–8.
37. Esteves SC, Conforti A, Sunkara SK, Carbone L, Picarelli S, Vaiarelli A, et al. Improving reporting of clinical studies using the POSEIDON criteria: POSORT guidelines. *Front Endocrinol (Lausanne)*. 2021;12:587051.
38. Esteves SC, Yarali H, Vuong LN, Conforti A, Humaidan P, Alviggi C. POSEIDON groups and their distinct reproductive outcomes: effectiveness and cost-effectiveness insights from real-world data research. *Best Pract Res Clin Obstet Gynaecol*. 2022;S1521-6934(22)00080–3.
39. POSEIDON Group (Patient-Oriented Strategies Encompassing Individualized Oocyte Number), Alviggi C, Andersen CY, Buehler K, Conforti A, De Placido G, et al. A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertil Steril*. 2016;105:1452–3.
40. Bozdag G, Polat M, Yarali I, Yarali H. Live birth rates in various subgroups of poor ovarian responders fulfilling the Bologna criteria. *Reprod Biomed Online*. 2017;34:639–44.
41. Romito A, Bardhi E, Errazuriz J, Blockeel C, Santos-Ribeiro S, Vos MD, et al. Heterogeneity among poor ovarian responders according to Bologna criteria results in diverging cumulative live birth rates. *Front Endocrinol (Lausanne)*. 2020;11:208.
42. Humaidan P, Chin W, Rogoff D, D'Hooghe T, Longobardi S, Hubbard J, et al. Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. *Hum Reprod*. 2017;32:544–55.
43. Leher P, Chin W, Schertz J, D'Hooghe T, Alviggi C, Humaidan P. Predicting live birth for poor ovarian responders: the PROsPeR concept. *Reprod Biomed Online*. 2018;37:43–52.
44. Leher P, Arvis P, Avril C, Massin N, Parinaud J, Porcu G, et al. A large observational data study supporting the PROsPeR score classification in poor ovarian responders according to live birth outcome. *Hum Reprod*. 2021;36:1600–10.
45. Arvis P, Massin N, Leher P. Effect of recombinant LH supplementation on cumulative live birth rate compared with FSH alone in poor ovarian responders: a large, real-world study. *Reprod Biomed Online*. 2021;42:546–54.
46. Alviggi C, Conforti A, Esteves SC, Vallone R, Venturella R, Staiano S, et al. Understanding ovarian hypo-response to exogenous gonadotropin in ovarian stimulation and its new proposed marker-the Follicle-To-Oocyte (FOI) index. *Front Endocrinol (Lausanne)*. 2018;9:589.
47. Ferraretti AP, Gianaroli L, Magli MC, D'angelo A, Farfalli V, Montanaro N. Exogenous luteinizing hormone in controlled ovarian hyperstimulation for assisted reproduction techniques. *Fertil Steril*. 2004;82:1521–6.
48. De Placido G, Alviggi C, Perino A, Strina I, Lisi F, Fasolino A, et al. Recombinant human LH supplementation versus recombinant human FSH (rFSH) step-up protocol during controlled ovarian stimulation in normogonadotrophic women with initial inadequate ovarian response to rFSH. A multicentre, prospective, randomized controlled trial. *Hum Reprod*. 2005;20:390–6.
49. Conforti A, Esteves SC, Picarelli S, Iorio G, Rania E, Zullo F, et al. Novel approaches for diagnosis and management of low prognosis patients in assisted reproductive technology: the POSEIDON concept. *Panminerva Med*. 2019;61:24–9.
50. Humaidan P, La Marca A, Alviggi C, Esteves SC, Haahr T. Future perspectives of POSEIDON stratification for clinical practice and research. *Front Endocrinol (Lausanne)*. 2019;10:439.
51. Yazıcı Yılmaz F, Gökemli H, Çolakoglu MC, Aktan M, Gezginç K. The evaluation of recombinant LH supplementation in patients with suboptimal response to recombinant FSH undergoing IVF treatment with GnRH agonist down-regulation. *Gynecol Endocrinol*. 2015;31:141–4.
52. Conforti A, Esteves SC, Di Rella F, Strina I, De Rosa P, Fiorenza A, et al. The role of recombinant LH in women with hypo-response to controlled ovarian stimulation: a systematic review and meta-analysis. *Reprod Biol Endocrinol*. 2019;17:18.
53. Alviggi C, Clarizia R, Pettersson K, Mollo A, Humaidan P, Strina I, et al. Suboptimal response to GnRH long protocol is associated with a common LH polymorphism. *Reprod Biomed Online*. 2011;22(Suppl 1):S67–72.
54. Alviggi C, Pettersson K, Longobardi S, Andersen CY, Conforti A, De Rosa P, et al. A common polymorphic allele of the LH beta-subunit gene is associated with higher exogenous FSH consumption during controlled ovarian stimulation for assisted reproductive technology. *Reprod Biol Endocrinol*. 2013;11:51–51.
55. Ku Y, Hong MA, Chae SJ, Lim KS, Lee W-D, Lim JH, et al. The effects of luteinising hormone gene polymorphism on the outcomes of in vitro fertilisation and embryo transfer. *J Obstet Gynaecol*. 2021;41:1092–6.
56. Barmat LI, Chantilis SJ, Hurst BS, Dickey RP. A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization. *Fertil Steril*. 2005;83:321–30.
57. Kol S. LH supplementation in ovarian stimulation for IVF: the individual, LH deficient, patient perspective. *Gynecol Obstet Invest*. 2020;85:307–11.
58. Garcia-Velasco JA, Coelingh Bennink HJT, Epifanio R, Escudero E, Pellicer A, Simón C. High-dose recombinant LH add-back strategy using high-dose GnRH antagonist is an innovative protocol compared with standard GnRH antagonist. *Reprod Biomed Online*. 2007;15:280–7.

59. Ramaraju GA, Cheemakurthi R, Prathigudupu K, Balabomma KL, Kalagara M, Thota S, et al. Role of Lh polymorphisms and r-hLH supplementation in GnRH agonist treated ART cycles: a cross-sectional study. *Eur J Obstet Gynecol Reprod Biol.* 2018;222:119–25.
60. Ramaraju GA, Cheemakurthi R, Kalagara M, Prathigudupu K, Balabomma KL, Mahapatro P, et al. Effect of LHCGR gene polymorphism (rs2293275) on LH supplementation protocol outcomes in second IVF cycles: a retrospective study. *Front Endocrinol (Lausanne).* 2021;12:628169.
61. Kristensen SG, Mamsen LS, Jeppesen JV, Bøtkjær JA, Pors SE, Borgbo T, et al. Hallmarks of human small antral follicle development: implications for regulation of ovarian steroidogenesis and selection of the dominant follicle. *Front Endocrinol (Lausanne).* 2017;8:376.
62. Marchiani S, Tamburrino L, Benini F, Pallecchi M, Bignozzi C, Conforti A, et al. LH supplementation of ovarian stimulation protocols influences follicular fluid steroid composition contributing to the improvement of ovarian response in poor responder women. *Sci Rep.* 2020;10:12907.
63. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee. Female age-related fertility decline. *Comm Opin 589 Fertil Steril.* 2014;101:633–4.
64. Alviggi C, Humaidan P, Howles CM, Tredway D, Hillier SG. Biological versus chronological ovarian age: implications for assisted reproductive technology. *Reprod Biol Endocrinol.* 2009;7:101–101.
65. Wiweko B, Prawesti DMP, Hestiantoro A, Sumapraja K, Natadisastra M, Baziad A. Chronological age vs biological age: an age-related normogram for antral follicle count, FSH and anti-mullerian hormone. *J Assist Reprod Genet.* 2013;30:1563–7.
66. Esteves SC, Yerali H, Vuong LN, Carvalho JF, Özbek IY, Polat M, et al. Cumulative delivery rate per aspiration IVF/ICSI cycle in POSEIDON patients: a real-world evidence study of 9073 patients. *Hum Reprod.* 2021;36:2157–69.
67. Yang R, Zhang C, Chen L, Wang Y, Li R, Liu P, et al. Cumulative live birth rate of low prognosis patients with POSEIDON stratification: a single-centre data analysis. *Reprod Biomed Online.* 2020;41:834–44.
68. Ata B, Kaplan B, Danzer H, Glassner M, Opsahl M, Tan SL, et al. Array CGH analysis shows that aneuploidy is not related to the number of embryos generated. *Reprod Biomed Online.* 2012;24:614–20.
69. Esteves SC, Carvalho JF, Martinhago CD, Melo AA, Bento FC, Humaidan P, et al. Estimation of age-dependent decrease in blastocyst euploidy by next generation sequencing: development of a novel prediction model. *Panminerva Med.* 2019;61:3–10.
70. Guligowska A, Chrzastek Z, Pawlikowski M, Pigłowska M, Pisarek H, Winczyk K, et al. Gonadotropins at advanced age - perhaps they are not so bad? Correlations between gonadotropins and sarcopenia indicators in older adults. *Front Endocrinol (Lausanne).* 2021;12:797243.
71. Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab.* 1995;80:1429–30.
72. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab.* 2005;90:3847–53.
73. Klein NA, Battaglia DE, Fujimoto VY, Davis GS, Bremner WJ, Soules MR. Reproductive aging: accelerated ovarian follicular development associated with a monotropic follicle-stimulating hormone rise in normal older women. *J Clin Endocrinol Metab.* 1996;81:1038–45.
74. Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. *Cochrane Database Syst Rev.* 2015;CD009749.
75. von Wolff M, Stute P, Eisenhut M, Marti U, Bitterlich N, Bersinger NA. Serum and follicular fluid testosterone concentrations do not correlate, questioning the impact of androgen supplementation on the follicular endocrine milieu. *Reprod Biomed Online.* 2017;35:616–23.
76. von Wolff M, Kollmann Z, Flück CE, Stute P, Marti U, Weiss B, et al. Gonadotrophin stimulation for in vitro fertilization significantly alters the hormone milieu in follicular fluid: a comparative study between natural cycle IVF and conventional IVF. *Hum Reprod.* 2014;29:1049–57.
77. Vuong TNL, Phung HT, Ho MT. Recombinant follicle-stimulating hormone and recombinant luteinizing hormone versus recombinant follicle-stimulating hormone alone during GnRH antagonist ovarian stimulation in patients aged ≥ 35 years: a randomized controlled trial. *Hum Reprod.* 2015;30:1188–95.
78. Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Pellicer A. Impact of luteinizing hormone administration on gonadotropin-releasing hormone antagonist cycles: an age-adjusted analysis. *Fertil Steril.* 2011;95:1031–6.
79. König TE, van der Houwen LEE, Overbeek A, Hendriks ML, Beutler-Beemsterboer SN, Kuchenbecker WKH, et al. Recombinant LH supplementation to a standard GnRH antagonist protocol in women of 35 years or older undergoing IVF/ICSI: a randomized controlled multicentre study. *Hum Reprod.* 2013;28:2804–12.
80. Conforti A, Esteves SC, Humaidan P, Longobardi S, D'Hooghe T, Orvieto R, et al. Recombinant human luteinizing hormone co-treatment in ovarian stimulation for assisted reproductive technology in women of advanced reproductive age: a systematic review and meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol.* 2021;19:91.
81. Arroyo A, Kim B, Yeh J. Luteinizing hormone action in human oocyte maturation and quality: signaling pathways, regulation, and clinical impact. *Reprod Sci.* 2020;27:1223–52.
82. Mendoza C, Ruiz-Requena E, Ortega E, Cremades N, Martinez F, Bernabeu R, et al. Follicular fluid markers of oocyte developmental potential. *Hum Reprod.* 2002;17:1017–22.
83. Tesarik J, Hazout A, Mendoza C. Luteinizing hormone affects uterine receptivity independently of ovarian function. *Reprod Biomed Online.* 2003;7:59–64.
84. Herrler A, von Rango U, Beier HM. Embryo-maternal signalling: how the embryo starts talking to its mother to accomplish implantation. *Reprod Biomed Online.* 2003;6:244–56.
85. Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Jenkins J, et al. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. *Hum Reprod.* 2010;25:2092–100.
86. Xu B, Li Z, Zhang H, Jin L, Li Y, Ai J, et al. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of more than 10,000 cycles. *Fertil Steril.* 2012;97:1321–7.e1–4.
87. Werner MD, Forman EJ, Hong KH, Fransasiak JM, Molinaro TA, Scott RT. Defining the sweet spot for administered luteinizing hormone-to-follicle-stimulating hormone gonadotropin ratios during ovarian stimulation to protect against a clinically significant late follicular increase in progesterone: an analysis of 10,280 first in vitro fertilization cycles. *Fertil Steril.* 2014;102:1312–7.
88. Smitz J, Andersen AN, Devroey P, Arce J-C, MERIT Group. Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinant FSH in IVF patients. *Hum Reprod.* 2007;22:676–87.
89. Friis Wang N, Skouby SO, Humaidan P, Andersen CY. Response to ovulation trigger is correlated to late follicular phase progesterone levels: a hypothesis explaining reduced reproductive outcomes caused by increased late follicular progesterone rise. *Hum Reprod.* 2019;34:942–8.
90. Filicori M, Cognigni GE, Samara A, Melappioni S, Perri T, Cantelli B, et al. The use of LH activity to drive folliculogenesis: exploring uncharted territories in ovulation induction. *Hum Reprod Update.* 2002;8:543–57.
91. Hugues JN. Impact of LH activity supplementation on serum progesterone levels during controlled ovarian stimulation: a systematic review. *Hum Reprod.* 2012;27:232–43.
92. Rahman A, Francomano D, Sagnella F, Lisi F, Manna C. The effect on clinical results of adding recombinant LH in late phase of ovarian stimulation of patients with repeated implantation failure: a pilot study. *Eur Rev Med Pharmacol Sci.* 2017;21:5485–90.
93. Krause BT, Ohlinger R, Haase A. Lutropin alpha, recombinant human luteinizing hormone, for the stimulation of follicular development in profoundly LH-deficient hypogonadotropic hypogonadal women: a review. *Biologics.* 2009;3:337–47.
94. Carone D, Caropreso C, Vitti A, Chiappetta R. Efficacy of different gonadotropin combinations to support ovulation induction in WHO type I anovulation infertility: clinical evidences of human recombinant FSH/human recombinant LH in a 2:1 ratio and highly purified human menopausal gonadotropin stimulation protocols. *J Endocrinol Invest.* 2012;35:996–1002.
95. The European Recombinant Human LH Study Group. Recombinant human luteinizing hormone (LH) to support recombinant human follicle-stimulating hormone (FSH)-induced follicular development in

- LH- and FSH-deficient anovulatory women: a dose-finding study. *J Clin Endocrinol Metab.* 1998;83:1507–14.
96. Shoham Z, Mannaerts B, Insler V, Coelingh-Bennink H. Induction of follicular growth using recombinant human follicle-stimulating hormone in two volunteer women with hypogonadotropic hypogonadism. *Fertil Steril.* 1993;59:738–42.
 97. Shoham Z, Balen A, Patel A, Jacobs HS. Results of ovulation induction using human menopausal gonadotropin or purified follicle-stimulating hormone in hypogonadotropic hypogonadism patients. *Fertil Steril.* 1991;56:1048–53.
 98. Burgués S, Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism. The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: evidence from a multicentre study in Spain. *Hum Reprod.* 2001;16:2525–32.
 99. Huseyin K, Berk B, Tolga K, Eser O, Ali G, Murat A. Management of ovulation induction and intrauterine insemination in infertile patients with hypogonadotropic hypogonadism. *J Gynecol Obstet Hum Reprod.* 2019;48:833–8.
 100. La Marca A, Longo M. Extended LH administration as a strategy to increase the pool of recruitable antral follicles in hypothalamic amenorrhea: evidence from a case series. *Hum Reprod.* 2022;37:2655–61.

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