Is there a need for recombinant human luteinizing hormone (lutropin alfa) supplementation in ovarian stimulation for assisted reproduction?

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Luteinizing hormone is now available as the recombinant product, lutropin alfa for the treatment of female infertility. It is necessary in the natural process of follicular growth and maturation. It is not yet clear which patients really benefit from the addition of this medication to conventional gonadotropin stimulation procedures in infertility treatment. Certainly, it has a proven benefit in patients suffering from hypogonadotropic hypogonadism (WHO I). Others may be older patients, patients with a profound gonadotropin suppression stimulated in long gonadotropin-releasing hormone agonist protocols, or patients with poor ovarian response to conventional stimulation strategies. The available data are reviewed herein.

Keywords: gonadotropin, hypogonadism, hypogonadotrophic, lutropin alfa, ovarian stimulation, poor response, recombinant technology

future medicine

Luteinizing hormone & oocyte maturation

It is well documented that in women with regular cycles, a basal luteinizing hormone (LH) concentration is secreted throughout the early to mid-follicular phases of the cycle, followed by a midcycle LH surge that triggers final oocyte maturation [1]. Gougeon reported that oocyte maturation is not a process that occurs in one menstrual cycle, but the end point of an almost 1-year period in the face of repeated cycles of changing gonadotropin levels [2]. The first months of oocyte development up to the late secondary follicle are follicle-stimulating hormone (FSH) independent [3], but the influence of FSH increases during later stages. However, the recruitment of follicles, selection of a leading follicle and ovulation are the result of the combined effects of FSH and LH. The so-called two-cell-two-gonadotropin theory means that LH stimulates the theca cell layer to secrete androgens, which diffuse to the granulosa cells and are aromatized to estrogens under the influence of FSH [4]. Therefore, a balance between these two gonadotropins is necessary to achieve a regular ovulatory cycle.

This theory was recently revisited as it has been demonstrated that LH receptors are expressed by granulosa cells during the intermediate follicular phase [5–7]. This means that LH directly contributes to optimizing growth and steroidogenesis of the leading follicle and favors atresia of small follicles. Therefore, using these receptors, LH has an influence not only on the theca cells but also on the granulosa cell layer [8].

Detrimental effects of high LH levels have been described in women with polycystic ovary syndrome (PCOS) who showed disrupted follicular maturation and often multiple small follicles on ultrasound [9]. Actual data regarding the relationship between PCOS and insulin resistance have demonstrated that the high LH level in these cases is an epiphenomenon of insulin resistance and that the latter could be the reason for the higher abortion rates in PCOS patients. Using insulin-sensitizing agents may therefore be an alternative to increase treatment efficacy [10]. However, the problem of LH and disturbed folliculogenesis in PCOS is not directly comparable due to additional variables (i.e., insulin resistance and hyperandrogenemia) influencing ovarian function.

Howles and MacNamee suggested an 'LH window' for normal follicle growth and concluded that follicle atresia and premature oocyte maturation would occur if LH levels exceeded this window [11].

Starting from this knowledge, later *in vitro* studies established the so-called 'ceiling' level of LH and the 'LH therapeutic window' [12–14]. It postulates that there is not only a threshold requirement for LH but also a ceiling level beyond which LH might be deleterious to ovarian stimulation [15,16]. Tesarik and Mendoza obtained the same findings in an oocyte-donation model [17]. In their study, donors with a deeply suppressed pituitary LH (<1 IU/l) had significantly more mature oocytes, good-quality embryos and a higher implantation rate after supplementation of exogenous LH. This was in contrast to supplemented donors with a prestimulation serum LH level of 1 IU/l or greater.

The LH ceiling concept

It has been demonstrated in an LH dose-finding study in WHO class I infertile women (hypogonadotrophic, hypogonadal patients) that ovarian

stimulation with 225 IU recombinant human (r-h)LH in combination with r-hFSH 150 IU/day led to fewer follicles in comparison with r-hLH 75 IU [18]. The negative influence of high LH levels on follicular maturation was confirmed in two randomized, placebo-controlled studies [19].

A recent study further supported the LH ceiling theory and confirmed that, considering a fine balance between FSH and LH, both gonadotropins are necessary during follicular development [20]. Hugues and colleagues concluded from their study that in patients over-responding to FSH during ovarian stimulation, doses of up to r-hLH 660 IU/day appear to increase the proportion of patients developing a single dominant follicle (≥16 mm) [20]. The proportion of patients with a single dominant follicle was increased from 13.3% in the placebo group to 32.1% in the r-hLH 660 IU group ($p = 0.048$), demonstrating the ability of LH to influence the development of the follicular cohort.

It is especially interesting when taking into account the data published by Filicori and colleagues [21,22]. They postulated that human chorionic gonadotropin (hCG) 400 IU/day in the late stimulation phase of a long gonadotropin-releasing hormone (GnRH) agonist/r-hFSH protocol may result in a lower oocyte yield and premature luteinization. In contrast, hCG 100 or 200 IU/day lowered the r-hFSH consumption and increased the number of mature follicles and oocytes retrieved. Stokman and colleagues compared the bioactivity of LH and hCG and found hCG 6 IU was equivalent to approximately 50 IU of LH (ratio approximately 1:8) [23]. Transferred to the data by Filicori and colleagues, hCG 400 IU is equivalent to approximately 3200 IU of LH [21]. In conclusion, the cited studies described different LH ceiling levels (225–660 to 3200 IU/day). These differences are a matter of debate and must be the focus of further studies.

LH & ovarian stimulation

From experiences with ovarian stimulation in hypogonadotrophic, hypogonadal patients, the importance of an LH threshold that must be exceeded to mature normal ovarian follicles is known. One possible stimulating agent is urinary human menopausal gonadotropin (hMG), but during the last few years, all necessary components (FSH, LH and hCG) have become available as recombinant agents. A trial to stimulate WHO I patients with r-hFSH alone resulted in a normal follicular growth but low estradiol levels (hCG 228 pg/ml/day, seven oocytes retrieved, endometrial thickness 5 mm) and a low fertilization rate of 28% (2/7). The fertilization rate increased to 93% (13/14) using only hMG (estradiol hCG 5073 pg/ml/day, 14 oocytes retrieved, endometrial thickness 10 mm), which proves the necessity of LH for ovarian stimulation in WHO I patients [24]. The efficacy of an exogenous recombinant LH preparation was first described some years ago [25].

In another study, different r-hLH dosages were added to r-hFSH for ovarian stimulation in WHO I patients [18]. A total of 38 patients (28 with primary and 10 with secondary hypogonadotrophic hypogonadism) were prospectively randomized for ovarian stimulation with either r-hFSH in a fixed dose of 150 IU/day alone or with the addition of different doses of r-hLH (25, 75 or 225 IU). Ovarian stimulation was continued for up to 20 days. Ovulation was induced with urine (u)-hCG 10,000 IU when a follicle reached at least 17 mm in diameter. Treatment with higher doses of LH (75 and 225 IU) resulted in a higher number of follicles compared with the group without LH or with a low LH dose (25 IU). Furthermore, estradiol level increased with the LH dose and a positive influence on the endometrium was documented. The authors concluded from their data that a dose of r-hFSH 150 IU and r-hLH 75 IU led to an optimal ovarian reaction.

Patients stimulated in a long GnRH-agonist protocol are said to be in a comparable situation to women with hypogonadotrophic hypogonadism (WHO I). In this protocol, downregulation of the hypophysis with a GnRH agonist starts in the late luteal phase, followed by ovarian stimulation after achieving hypogonadal status. The LH level in these patients is often below the lower detection level of the LH assay. In contrast to the hypogonadotrophic patient, ovaries of patients treated in a long protocol are free from the influence of LH for days, whereas hypogonadotrophic hypogonadal patients may be without the influence of LH for many years. Therefore, it is not appropriate to extrapolate data directly from one group to the other and separate studies are necessary to come to final conclusions.

Low LH levels in long GnRH-agonist cycles

Studies analyzing the reproductive outcome in patients treated with highly purified urinary FSH (u-FSH-HP) or r-hFSH have demonstrated different results with different LH

Table 1. Studies dealing with the influence of LH levels on reproductive outcome in patients stimulated with FSH in a long GnRH-agonist protocol.

Study design	Protocol	LH measurements	LH level (IU/l)	n		Effects	Ref.
				LH ↑	LH ↓		
Retrospective	Long luteal protocol (buserelin 4 x 200 µg intranasal/day) + u-FSH-HP	Day 7	≤0.7 ≤0.7	125 160	271 536	Rate of low response ↑ Duration of gonadotropin stimulation ↑ Estradiol (hCG day) ↓ Number of oocytes ↓ Estradiol (hCG day) ↓	[26]
Prospective	Long luteal protocol (buserelin 4 x 200 µg intranasal/day) + u-FSH-HP	Day 7, 8 or 9	≤0.5	20	41	Number of oocytes (trend) ↓ Fertilization rate ↓ Supernumerary embryos ↓ Normal blastocyst rate	[29]
Retrospective	Long luteal protocol (leuprolide acetate 0.5 mg/day s.c.) + r-hFSH	Day 8	<0.5	98	102	Estradiol (hCG day) ↓ Similar clinical pregnancy rate Abortion rate ↑	[30]
Retrospective	Long luteal protocol (leuprolide acetate 0.5/0.25 mg/day s.c.) + r-hFSH	Day 5 (4–5 values averaged starting on day 5)	<3.0	116	50	Fertilization rate ↓ Biochemical abortions (trend) ↑	[31]
Prospective	Long luteal protocol (leuprolide acetate 0.5 mg/day s.c.) + r-hFSH	Day 6 and 9	≤2.0	95	77	Duration of gonadotropin stimulation ↓ Estradiol (hCG day) ↓ Number of oocytes ↓ Pregnancy rates ↓	[32]
Retrospective, controlled	Long luteal protocol (leuprolide acetate 1.0/0.5 mg/day s.c.) + r-hFSH	Day 7	<0.5 <0.7 <1.0	10 21 44	134 123 100	No effects	[33]
Retrospective	Long luteal protocol (leuprolide acetate 0.8/0.4 mg/day s.c.) + r-hFSH	Day 8	≤0.5 0.51–1.0 1.01–1.5 >1.5	24 108 38 37	183 75 37 –	Number of fertilized oocytes ↓ Fertilization rate ↓*	[34]

**Negative effects with LH levels > 1.5 IU/l were more severe than those corresponding to low LH levels: significantly lower implantation rate than in patients with LH ≤ 0.5 IU/l and significantly lower clinical pregnancy rate compared with LH 0.5–1.0 IU/l.*
FSH: Follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; LH: Luteinizing hormone; r-h: Recombinant human; s.c.: Subcutaneous; u-FSH-HP: Highly purified urinary FSH.

thresholds [26]. This is in contrast to the data from the LH dose-finding study [18] as well as the observation that the results using r-hFSH are better than those obtained using u-FSH-HP and at least as good as those with hMG [27,28]. Different observational studies, including patients stimulated with FSH in long GnRH-agonist protocols, examined the influence of serum LH level on reproductive outcome (Table 1) [26,29–34].

The conflicting results can be caused by the use of different types and amounts of GnRH agonists, modes of administration and the detection limit of the LH assay used, making it difficult to compare studies performed in individual centers. However, there may be a threshold below which LH needs to be replaced to guarantee optimal ovarian stimulation. The main question is: how low is this threshold and how often does it occur?

One can assume that it is a problem of a small subgroup of patients in long GnRH-agonist protocols. Furthermore, it has been established that less than 1% of LH receptors must be occupied to achieve an optimal ovarian response [35].

Balasch and colleagues analyzed different LH threshold levels (0.5, 0.7 and 1.0 U/l) in relation to the abortion and pregnancy rates in an *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) program [33]. They found no significant difference between the groups regarding these two parameters.

The problem seems to be an empirical addition of exogenous LH, which may negatively influence the therapeutic outcome. This conclusion was supported by another study comparing a GnRH-agonist long protocol, either with r-hFSH alone or in combination with r-hLH [36]. The duration of ovarian stimulation and estradiol levels on the day of hCG were not statistically different in both groups. But there was a higher rate of metaphase II oocytes in the r-hFSH group, with a higher fertilization rate and a lower rate of fertilization failure.

The data were confirmed, for example, by Humaidan and colleagues [34]. They too described, in a long protocol, that optimal results were achieved in patients whose LH levels were in the range 0.51–1.5 IU/l on cycle day 8. If the LH levels increased above this point, the patients had a lower pregnancy rate. The outcome was less favorable than that found in patients with LH levels of 0.5 IU/l or lower. Obviously, a functional deficit of LH, more than an LH excess, could lead to a suboptimal result. They suggest that a discrepancy between circulating LH levels and LH bioactivity may exist *in vivo*. Women displaying high LH levels may have a less active form, requiring exogenous LH. These conflicting results further indicate that a certain threshold level of LH might be required in endocrinologically healthy patients during ovarian stimulation in GnRH-agonist protocols. If LH falls below this cut-off, poor results are the consequence. However, the discrepancies among the studies do not allow the definition of a clinically useful cut-off level that identifies women who require LH supplementation.

Ho and colleagues described that a higher FSH:LH ratio (≥3) on the first day of stimulation following administration of a GnRH agonist in a long-luteal protocol is associated with a poor response [37]. In a retrospective study of 240 short GnRH-agonist cycles, the implantation rates were lower if the LH level on stimulation day 8 was 5 IU/l or lower [38]. Explanations for this phenomenon could be a resulting excess of androgens, which may subsequently disrupt follicular and oocyte maturation [33,39].

Importance of flexible LH administration during ovarian stimulation in long GnRH agonist protocols

After the introduction of r-hLH, many studies have been performed dealing with the key question: is LH supplementation in GnRH-agonist protocols useful? In contrast to urinary preparations of hMG containing LH with a high batch-to-batch variability in hCG and LH content, the r-hLH filled by mass allows a precise titration of the individual amount of LH necessary during ovarian stimulation with r-hFSH. Two interesting subgroups of patients initially studied were poor responders [40] and patients who respond inadequately to FSH stimulation [41,42]. In addition, Marrs and colleagues [43] and Humaidan and colleagues [44] postulated from their results that patients aged 35 years or older benefited from LH supplementation in terms of increasing the number of mature oocytes retrieved.

LH supplementation in potentially normal responders

Three different studies clearly indicated that LH supplementation is not required in all women [43–45]. Sills and colleagues compared the IVF outcome in two age-matched groups receiving either FSH-HP alone (n = 17) or FSH-HP plus r-hLH (n = 14) in a long GnRH-agonist protocol (leuprolide acetate 1 or 0.5 mg/day subcutaneously) prospectively [45]. They found a trend toward better pregnancy outcomes in patients stimulated with FSH-HP alone (mean implantation rate 26.9 vs 11.9%; clinicial pregnancy rate/initiated cycle: 64.7 vs 35.7%). Due to the small study groups, these differences did not reach statistical significance. In another prospective, randomized study, 231 normogonadotrophic patients were stimulated with either r-hFSH alone (n = 115) or r-hFSH plus r-hLH in a ratio of 2:1 (n = 116) in a long GnRH-agonist protocol [44]. These groups did not differ with respect to pregnancy rate. This result was confirmed by Marrs and colleagues, who also compared women stimulated with r-hFSH alone (n = 219) versus r-hFSH plus r-hLH (n = 212) [43].

Tarlatzis and colleagues performed a double-blind, randomized, prospective study in young normogonadotrophic women and compared ovarian stimulation with r-hFSH alone versus r-hFSH with additional r-hLH for the last few days of FSH stimulation in a long GnRH-agonist protocol [46]. They found no significant difference between the groups in all end points evaluated. These results confirm that only subgroups (as mentioned above) may benefit from r-hLH supplementation.

One difference between the studies was that LH was given at doses of 75–150 IU/day starting on different stimulation days. Nevertheless,

all these studies were unable to demonstrate a clinical benefit of LH supplementation in normal responders. In contrast, in another prospective, randomized study (stimulation with r-hFSH vs r-hFSH plus hMG), LH supplementation increased the number of mature oocytes, fertilized oocytes and transferable embryos [47].

LH supplementation in patients aged 35 years or older

Humaidan and colleagues described significantly increased implantation rates in a subgroup of women aged 35 years or older supplemented with r-hLH in a long GnRH-agonist protocol [44]. The total FSH consumption necessary was significantly lower in comparison with nonsupplemented controls. An additional subgroup of women with LH levels higher than 1.99 IU/l on stimulation day 8 had a benefit with regard to the treatment outcome.

Patients in the older age group may need LH supplementation to achieve good ovarian response and follicular maturation. Endogenous LH, as well as FSH, levels increase with age and the onset of menopause [48]. This may be caused by a decreased number of functional LH receptors [49] and a different biological activity of endogenous LH [50–53], resulting in an increased resistance to LH-mediated processes [54].

Fabregues and colleagues could not confirm the benefit of r-hLH supplementation in this subgroup. In a prospective, randomized study, stimulation with r-hFSH alone or r-hFSH plus r-hLH in a long GnRH-agonist protocol (60 vs 60 patients) was compared [55]. Administration of r-hLH did not increase ovarian response and implantation rates in infertile women aged 35 years or older.

LH supplementation in women who abnormally respond to FSH

A further subgroup in whom LH supplementation could be beneficial is patients suffering from hypogonadotrophic hypogonadism (natural or induced). The latter group includes patients with GnRH-agonist depot preparations, especially in ultralong protocols of several months. It is well known that the degree of LH suppression in GnRH-agonist protocols varies between different preparations [56]. One can further speculate that patients with profound LH suppression may benefit from LH supplementation. In this context, the potential detrimental effect of excessive LH levels if a patient is oversupplemented must be carefully considered.

De Placido and colleagues performed three prospective, randomized studies on normogonadotrophic IVF patients stimulated with FSH in a long GnRH-agonist depot protocol [41,57,58]. In a subgroup of low responders to stimulation (estradiol < 180 pg/ml and no follicle > 10 mm on day 8 of FSH stimulation), they found a significant increase in the number of retrieved oocytes with increasing doses of LH. The number of oocytes was comparable to a control group after using 150 IU r-hLH [57]. In another study, they tested whether using 150 IU r-hLH from day 8 in a similar population of patients was associated with an improvement in outcomes compared with increasing the doses of r-hFSH [58]. Surprisingly, adding r-hLH, but not increasing r-hFSH, led to an improved clinical pregnancy outcome. Lisi and colleagues added r-hLH to r-FSH stimulation in IVF cycles (n = 12) of patients who needed more than 3000 IU r-hFSH in further stimulations without LH (n = 17) [40]. The result was significantly higher fertilization (60.9 vs 86%) and clinical pregnancy rates (5.9 vs 50%). De Placido and colleagues also suggested from their study that LH supplementation improves the ovarian outcome in patients characterized by an inadequate initial response to r-hFSH therapy in a long GnRH-agonist depot protocol [41]. In a subgroup of patients without follicles larger than 10 mm and an estradiol concentration of 0.6 pmol/ml or lower on stimulation day 8, the investigators added hMG 150 IU/day. The consequences were significantly higher estradiol concentrations on the day of hCG treatment and significantly more oocytes retrieved in comparison with controls, which were further stimulated with r-hFSH alone. Intriguingly, the addition of a small amount of r-hLH (75–150 IU/day), but not hMG, was able to rescue oocyte competence to produce viable embryos (inclusion criteria: plateau on follicular growth between cycle day 7 and 10) [42].

In this context, it has to be underlined that in almost all of these trials, women who benefited from LH supplementation had circulating LH levels comparable with those who normally responded to r-hFSH. This evidence is consistent with the previously mentioned data by Humaidan and colleagues [44], and reinforces the idea of possible discrepancies between immunoreactive and bioactive LH. Interestingly, some authors have recently suggested an association between ovarian resistance to r-hFSH monotherapy and the presence of an LH polymorphism (*V-βLH*) in normogonadotrophic women undergoing a GnRH-agonist long

Table 2. Studies dealing with the influence of LH supplementation on reproductive outcome in patients stimulated with FSH in a GnRH-antagonist protocol.

Study design	Protocol	n		Effects	Ref.
		With r-hLH	Without r-hLH		
Prospective	Single-dose GnRH antagonist (cetrorelix 3.0 mg when the leading follicle reached 14–16 mm) + r-hFSH	114	104	Higher estradiol level in the group with LH supplementation ($p < 0.001$) Similar number of oocytes/embryos Similar delivery and implantation rate	[63]
Prospective	Single-dose GnRH antagonist (cetrorelix 3.0 mg on stimulation day 7) + r-hFSH	21	21	Higher concentration of estradiol per follicle level in the group with LH supplementation ($p = 0.022$) Similar duration of stimulation Similar total dose of r-hFSH Similar number of oocytes/embryos Similar clinical pregnancy and implantation rate	[64]
Prospective	Multiple dose GnRH antagonist (cetrorelix 0.25 mg/day from stimulation day 6 up to and including the day of hCG) + r-hFSH	62	65	Higher estradiol level in the group with LH supplementation ($p < 0.03$) Higher LH level in the group with LH supplementation ($p < 0.01$) Similar duration of stimulation Similar number of oocytes/embryos Similar clinical pregnancy and implantation rate	[65]

FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; LH: Luteinizing hormone; r-h: Recombinant human.

protocol [59]. This evidence suggests that women carrying a less effective form of LH, despite normogonadotrophism and regular ovulatory cycles, require higher FSH doses and/or LH supplementation during ovarian stimulation.

How can LH supplementation result in a positive effect? Foong and colleagues demonstrated that in low or poor responders during r-hFSH stimulation, intrafollicular estradiol was significantly lower and progesterone significantly higher in low and poor responders despite comparable peak estradiol levels to normal responders [60]. Concluding from these results, it seems that LH may have a beneficial effect through a mechanism that improves oocyte cytoplasmic maturation, either through estradiol or some other intraovarian factor. An additional effect on the endometrium itself cannot be excluded [61].

Importance of flexible LH administration during ovarian stimulation in GnRH antagonist protocols

Another controversial issue is the use of LH supplementation in patients receiving GnRH antagonists. This idea is related to the evidence that a rapid decline in both LH and estradiol concentration usually follows the administration of a GnRH antagonist. As a consequence, the oocyte/follicle unit may undergo dramatic and potentially detrimental changes due to the hormonal environment. On the other hand, a significantly higher pregnancy rate was described in patients with profound LH suppression (≤0.5 IU/l) on day 8 of stimulation (prospective, n = 116, r-hFSH 200 IU fixed from cycle day 2 and daily 0.25 mg GnRH antagonist from day 6 of stimulation) [62]. Some clinical trials have been designed in order to investigate the efficacy of LH supplementation in different subsets of patients treated with GnRH antagonists (Table 2) [63–65].

In spite of higher estradiol and LH levels on the day of hCG administration, no benefit of r-hLH supplementation in an unselected group of patients stimulated in a GnRH-antagonist protocol was found [63,65]. The only difference in patients stimulated with r-hFSH alone was a significantly lower concentration of estradiol per follicle [64].

In a prospective, randomized study De Placido and colleagues, patients at risk for a poor response (age ≥ 37 years or basal FSH on cycle day 2 ≥ 9 IU/l) were compared [66]. Patients were stimulated either in a short GnRH-agonist protocol

(r-hFSH 300 IU/day plus triptorelin 0.1 mg/day starting on cycle day 2, 150 IU r-hLH starting when the leading follicle reached 14 mm; n = 62) or a GnRH-antagonist protocol (r-hFSH 300 IU starting on cycle day 2, GnRH antagonist 0.125 mg/day for 2 days starting when the leading follicle reached 14 mm, thereafter GnRH antagonist 0.25 mg/day, r-hLH 150 IU/day starting on the first day of GnRH antagonist; n = 62). The mean number of metaphase II oocytes was significantly higher in the antagonist group (5.73 ± 3.57 vs 4.64 ± 2.23; $p < 0.05$). It is not possible to conclude from the study if this benefit was a result of the antagonist protocol itself or of the additional r-hLH. Implantation rate and ongoing pregnancy rate demonstrated no significant differences between the groups.

Conclusion

As very low levels of LH are necessary for sufficient follicular development, lutropin alfa allows precisely controlled LH supplementation in patients who need additional LH. This subgroup of patients are women with a profound LH suppression in long GnRH agonist cycles, older patients and patients with low ovarian response to gonadotropin stimulation.

Future perspective

Ovarian stimulation has not really changed since its beginning in the 1950s. There are two main steps: gonadotropin stimulation and subsequent hCG administration. What has changed is the variety of stimulation protocols that are now available, with the introduction of the GnRH agonist in the early 1980s and the GnRH antagonists in the late 1990s. Furthermore, the gonadotropins have become more pure, more consistent and optimally defined by modern manufacturing techniques. Future studies should address the question of which patients really benefit from certain amounts and types of gonadotropins. It may be possible to modify the gonadotropin molecules to achieve an optimal response in individual patients. The first steps in this direction have been completed with modification of the C-terminal peptide in FSH molecules to increase their half-life [67]. However, other modifications may substitute certain genomic individualities in patients, such as LH- or FSH-receptor anomalies. Recent studies have demonstrated that this approach may really result in an improved outcome for the patients [68,69].

It is possible that, in the future, we will be able to screen a patient on a basis of certain gonadotropin and receptor anomalies and initiate an individualized scheme of gonadotropin stimulation with not only individualized amounts of gonadotropins, but also with an individualized mixture of different gonadotropin isoforms.

Executive summary

- In the menstrual cycle, luteinizing hormone (LH) is important for follicle development and maturation.
- According to the two-cell-two-gonadotropin concept, LH has its major impact on the theca cells for the production of androgen precursors.
- A lower beneficial level of LH (threshold level) and a higher detrimental level of LH (ceiling level) has been suggested in the literature; however, these levels cannot yet be precisely defined.
- There are some groups of patients (hypogonadotrophic hypogonadism, WHO I) who benefit from LH supplementation, since they do not have any endogenous LH activity.
- Other groups, such as patients with severely suppressed levels of gonadotropins, especially LH, by the use of long-term gonadotropin-releasing hormone (GnRH)-agonist depot preparations, older patients, or patients with low response to conventional gonadotropin stimulation, may also benefit from LH supplementation.
- Overall, the data from prospective, randomized studies are not yet able to ideally define these subgroups.

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