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ASSISTED REPRODUCTION TECHNOLOGIES

The role of luteinizing hormone in the management of female infertility: A French Delphi consensus

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Abstract

Purpose To clarify clinical practice with regard to LH requirements and identify patient profiles that could benefit from luteinizing hormone (LH)-follicle-stimulating hormone co-treatment.

Methods In a Delphi survey, a scientific advisory board elaborated 28 statements on the role of luteinizing hormone (LH) in folliculogenesis ($n=7$ statements), the utility of LH for follicular development prior to ovulation induction/intrauterine insemination protocols ($n=3$), the utility of LH for follicular development prior to agonist or pretreated antagonist protocols in IVF ($n=6$), the source and type of LH activity ($n=3$), and patient profiles ($n=9$). These statements were reviewed and clarified by two pilot experts. A panel of 26 French ART experts voted in two rounds. Full consensus and consensus were defined respectively as 100% and > 66% agreement. Statements could be reformulated between the two rounds of voting.

Results A full consensus or a consensus was reached for 24 of the 28 statements. All the statements concerning the pathophysiological role of LH in folliculogenesis achieved a consensus. The experts endorsed the basic science and emphasized the need to consider inter-individual variability in the clinic. Recombinant human LH was considered to optimize outcomes in a range of patient profiles: a suboptimal ovarian response to IVF stimulation, desensitization following a long agonist protocol, advanced maternal age (> 35), polymorphisms, low body mass index, and women with hypogonadotropic hypogonadism.

Conclusions This Delphi consensus from a representative group of French experts provided real-world guidance on LH's crucial importance in folliculogenesis and the patient profiles for which LH is beneficial.

Keywords Delphi consensus · R-hLH · Folliculogenesis · Assisted reproductive technology · Ovarian response · IVF stimulation

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Introduction

Luteinizing hormone (LH) is essential for steroidogenesis, follicle growth, and oocyte maturation. Although basal folliculogenesis was classically considered to be gonadotropin-independent, recent data in humans demonstrate that gonadotropins have a critical role in follicular progression through the pre-antral stages. Indeed, the pre-antral stages are now considered to be gonadotropin-sensitive [1, 2]. In the later stages of folliculogenesis, interplay between follicle-stimulating hormone (FSH) and LH controls the final follicular growth of the antral follicles [1, 2]. In the early follicular phase, LH enhances the recruitment of antral follicles via the theca cells' androgen production, which induces the upregulation of FSH receptors. From the mid-follicular phase onwards and despite the decrease in FSH levels, the appearance of specific LH receptors on the granulosa cells promotes the final follicular maturation and survival of the dominant follicle via LH's anti-apoptotic effect [3, 4].

Historically, the use of LH in the management of female infertility has been disfavoured by the suboptimal outcomes of in vitro fertilization cycles in women with polycystic ovary syndrome — a condition often associated with elevated LH levels [4]. However, the relationship between levels of LH and IVF outcomes appears to be more complex than first thought [5]. A number of studies have highlighted the potential utility of recombinant human LH (r-hLH) in several patient profiles, including hypogonadotropic hypogonadism, LH deficiency, a suboptimal response to controlled ovarian stimulation, age 35, and a very low ovarian reserve [6–12]. However, the literature data on the use of LH by women aged 35 or over or by poor responders is controversial, patchy and/or unabundant.

In European countries and many other countries worldwide, treatment with r-hLH is authorized for the stimulation of follicular development in women with severe LH and FSH deficiencies, subject to the indications set out in the corresponding summary of product characteristics (European Medicines Agency [13]). In pivotal clinical trials, hypogonadotropic hypogonadism was defined as a baseline plasma concentration of endogenous LH below 1.2 IU/L. The health authorities updated the details of this indication in 2021: severe LH and FSH deficiencies no longer had to be defined solely by gonadotropin levels determined in lab assays. It is now acknowledged that a broad spectrum of acquired or congenital aetiologies for severe LH and FSH deficiencies may qualify a woman for treatment: these notably include intensive exercise and eating disorders (potentially resulting in a low body mass index), psychological stress, poorly controlled diabetes, thyroid hormone disorders, conditions affecting pituitary function (e.g. Sheehan's syndrome and prolactinomas), and gene polymorphisms in gonadotropins or their receptors [9, 14]. Furthermore, advanced maternal age might exacerbate an underlying LH dysfunction during ART, due to downregulation by a gonadotrophin-releasing hormone (GnRH) analogue [15]. However, a number of acknowledged areas of clinical disagreement remain. For example, the population of women aged 35 or over is likely to be heterogeneous, and the results of some studies have suggested that the 35–39 group and the 40 + group differ markedly in terms of clinical outcomes [16]. Furthermore, the use of "LH priming" in poor responders does not increase the number of oocytes but does appear to increase the clinical pregnancy rate [8, 17].

The objectives of the present Delphi study were to evaluate the impact of this change in the indication for LH, clarify current clinical practice with regard to LH requirement, and identify patient profiles that could benefit from co-treatment with LH and FSH. In the Delphi consensus method, a panel of experts give their opinions on a relevant issue [18, 19]. Based on the assumption that group judgements are more valid than isolated, individual judgements, the experts' opinions are aggregated in an anonymous, controlled, iterative process, and a consensus (full or partial) is sought. The Delphi method has been used extensively as a tool in health sciences (including reproductive medicine) to (i) prepare and evaluate clinical practice guidelines, (ii) form a consensus around clinical problems, and (iii) predict developments in the field [20–29]. Indeed, the use of LH in reproductive medicine has been addressed by several recent Delphi surveys in various countries worldwide [20, 30–32]. Here, a conventional, three-phase Delphi survey in France comprised an exhaustive literature review, statement development by a scientific advisory board (SAB), and a review of the statements by two pilot experts (Phase 1), a first round of voting on the statements by an expert panel (Phase 2), the reformulation of certain statements if required, and a second (final) round of voting on the statements (Phase 3). The panel members were all experienced specialist ART physicians, working in private-sector clinics or public-sector general and university hospitals from across France.

Materials and method

The Delphi survey: phase 1

Three of the investigators with expertise in gynaecology and endocrinology (IC, LJ, and JL, forming the project's SAB) exhaustively reviewed the literature in the field and then generated a set of statements on the pathophysiological role of LH in folliculogenesis and the indications of LH activity in the management of female infertility (Fig. 1).

The SAB members had been invited to participate in the Delphi survey by the study sponsor (Merck Serono SAS (Lyon, France)), in view of their clinical experience, publication records, and relevant contributions to congresses and meetings. The statements (in French) were composed on the basis of the

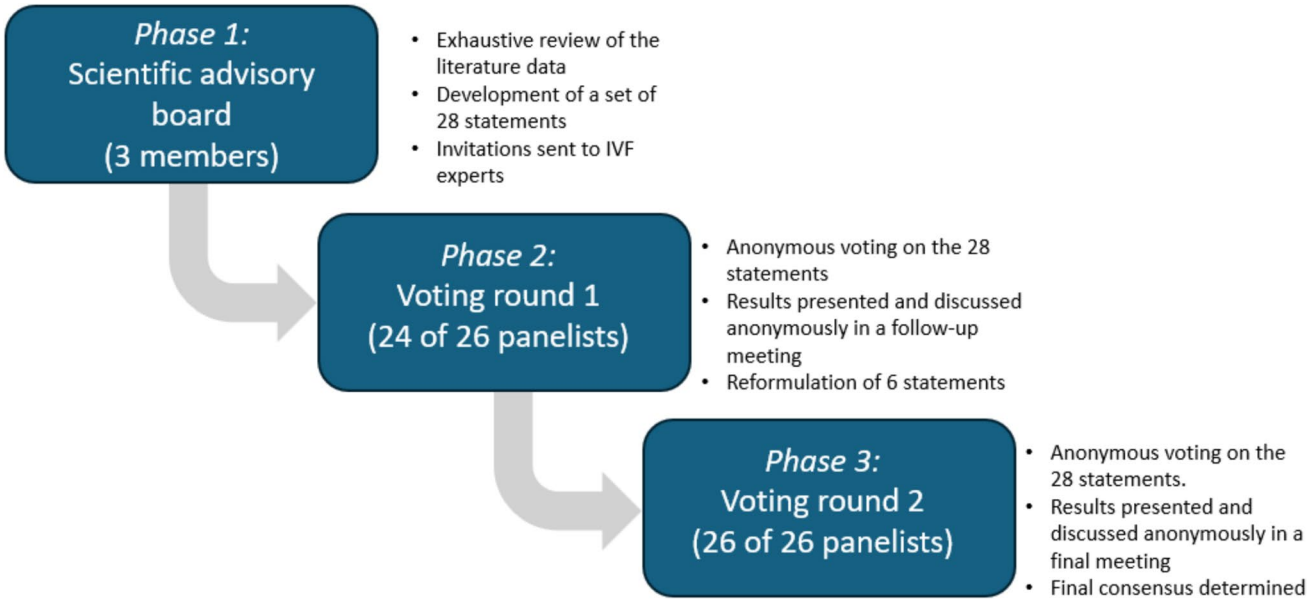

Fig. 1 The study design

latest scientific literature and the SAB members' knowledge and experience of clinical practice. Two pilot experts (BS and FO) were invited by the SAB to review and clarify (if required) the wording of the 28 statements before the start of Phase 2.

The Delphi survey: phase 2

Twenty-six other experts (both men and women, all with in-depth knowledge and experience of LH use, as judged by their clinical experience, publication records, and relevant contributions to congresses and meetings) were invited to join the Delphi expert panel. Particular care was taken to ensure that these expert men and women came from public- and private-sector IVF centres from all regions of France. In line with an evidence-based approach, all members of the expert panel were provided with an exhaustive list of publications on each statement. When choosing these publications, the members of the SAB considered the impact factor of the journal in which the study was published, the study design (notably RCTs and meta-analyses, when available), the sample size, and the date of the study.

During a three-week, online first round of voting held between April 30th and May 21 st, 2024, the members of the expert panel voted on their level of agreement with the 28 statements. Votes were based on the experts' experience and knowledge of the publications that they had received or were already familiar with. For each statement, the panellists voted anonymously and independently on a four-point Likert scale: "I strongly agree", "I moderately agree", "I moderately disagree", or "I fully disagree". Furthermore, each expert had to justify their choice by typing a free-text comment. The overall level of consensus was defined as follows: the proportion of panellists agreeing moderately or fully with a given statement was set to 100% for a full consensus, > 66% for a consensus, and < 66% for a lack of consensus. The consensus threshold of 66% was chosen by reference to the literature on Delphi surveys in reproductive medicine [21–23]. Statements with a full consensus in the first round of voting were accepted definitively; they were not included in the second round. All the other statements were voted on again, so that the panellists could change their mind (or not, as the case may be). After the first online voting period, the three SAB members and the available panellists met online on May 21 st, 2024, in order to present the voting results, discuss the comments, and clarify the statements if required. Meeting attendance and the discussions during the meeting were anonymous: questions and comments were sent via chat messages. During this discussion with the panellists, the SAB members were allowed to slightly revise a statement's wording, if required.

In Phase 3, the statements not having achieved a fully consensus (including those with a revised wording) were voted on a second time during a three-week, online round held between June 12th and July 4th, 2024. The three SAB members and the available panellists then met online on July 4th, 2024, in order to view and discuss the voting results.

The Delphi survey phases were coordinated by a clinical research organization (CEMKA (Bourg-la-Reine, France)). The survey was initiated and funded by Merck Serono SAS (Lyon, France). However, the study sponsor was not involved in the statement development, voting, or discussions between panellists. In line with the French legislation on opinion surveys, the study protocol did not require approval by an independent ethics committee.

Results

The survey procedures

The members of the SAB developed a set of 28 statements considered to be relevant (Tables 1, 2, 3, 4, 5). The statements concerned five areas: (i) the pathophysiological role of LH in folliculogenesis ($n=9$ statements), (ii) the utility of LH administration for follicular development in ovulation induction (OI)/intrauterine insemination (IUI) protocols ($n=3$), (iii) the utility of LH administration for follicular development in antagonist protocols with oral contraceptive pretreatment or in agonist protocols ($n=6$), (iv) the type and origin of the LH activity: urinary human menopausal gonadotrophins (hMGs) vs. recombinant gonadotrophins (co-treatment with r-hLH and r-hFSH) ($n=3$), and (v) patient profiles.

The SAB invited 29 experts to participate in the Delphi voting: 26 agreed (17 women and 9 men), and three refused. The 28 statements were submitted to the experts in voting round 1. Of the 26 experts who had agreed to participate in round 1, 24 voted: one expert encountered technical problems during the vote, and another failed to vote within the designated time period (Tables 1, 2, 3, 4, 5). In round 1, two statements achieved a full consensus, 19 achieved a consensus, and seven did not achieve a consensus but were retained for submission to the experts in voting round 2. Five statements (three of which had achieved a consensus in round 1) were reformulated during the subsequent discussion: statements 3e (75% agreement in round 1), 3f (46%), 4b (67%),

Table 1 The subset of statements on the pathophysiological role of LH in folliculogenesis, as developed by the SAB and submitted to two rounds of Delphi voting

Statement number	Statement	Level of agreement in round 1	Level of agreement in round 2	Outcome
1a	During folliculogenesis, LH (via androgens) is necessary for normal follicular growth	87%	96%	Consensus
1b	During folliculogenesis, an excess of LH is associated with follicular arrest	87%	96%	Consensus
1c	Harmonious steroidogenesis and folliculogenesis require a good balance between FSH and LH	92%	96%	Consensus
1d	LH has different actions at the start and at the end of the follicular phase: • At the start: LH contributes to the production of androgens (the substrates of oestradiol production and which stimulate folliculogenesis via the induction of FSH receptors) by the theca cells; • At the end: thanks to the appearance of specific receptors on granulosa cells, LH has an anti-apoptotic effect that keeps the follicles viable	96%	100%	Full consensus
1e	The half-life of hCG is longer than that of LH, which leads to internalization of the LH/hCG receptors	92%	100%	Full consensus
1f	Women of advanced maternal age have low levels of endogenous LH activity	88%	100%	Full consensus
1 g	There are polymorphisms of LH and the LH-hCG receptor that modify the requirement for LH activity in patients	100%[§]	100%[§]	Full consensus

[§] Statements with a 100% level of agreement in round 1 were not voted on again in round 2; however, the value of 100% in round 1 is carried over into the column for round 2

Table 2 The subset of statements on LH administration for follicular development followed by OI/IUI protocols, as developed by the SAB and submitted to two rounds of Delphi voting

Statement number	Statement	Level of agreement in round 1	Level of agreement in round 2	Outcome
2a	For patients with hypogonadotropic hypogonadism, the combined provision of FSH and LH in a 2:1 ratio is associated with optimal steroidogenesis and folliculogenesis	96%	100%	Full consensus
2b	For the great majority of ovulating patients, the LH requirements are covered and LH administration is not required outside IVF cycles	96%	96%	Consensus
2c	The use of a GnRH antagonist in an intrauterine insemination cycle does not produce a fall in LH activity that is long enough to require LH administration	83%	85%	Consensus

Table 3 The subset of statements on the LH administration for follicular development followed by agonist or pretreated antagonist protocols in IVF, as developed by the SAB and submitted to two rounds of Delphi voting

Statement number	Statement)	Level of agreement in round 1	Level of agreement in round 2	Outcome
3a	The long-term use of oral contraceptives can increase the likelihood of a hyporesponse in patients	67%	96%	Consensus
3b	It is essentially in long GnRH agonist protocols that a lack of LH activity and thus a need for LH are most likely	67%	88%	Consensus
3c	Assaying the plasma LH concentration alone is not sufficient for determining whether LH is needed	100%[§]	100%[§]	Full consensus
3d	A relative LH deficiency is reflected by a dissociation between hormone levels and ultrasound findings or as a lack of follicular recruitment, even when the reserve is satisfactory	87%	92%	Consensus
3e*	In an antagonist protocol without oral contraceptive pretreatment, it is not necessary to systematically administer LH to obtain an optimal response	75%	100%	Full consensus
3f*	Pretreatment with a combined oral contraceptive in an antagonist protocol can induce the same risk of LH deficiency as in a long agonist protocol, when the wash-out period is shorter than 5 days	46%	62%	No consensus

[*] Reformulated between rounds 1 and 2. See Supplementary Table 1. [§] Statements with a 100% level of agreement in round 1 were not voted on again in round 2; however, the value of 100% in round 1 is carried over into the column for round 2

Table 4 The subset of statements on the type and source of LH activity, as developed by the SAB and submitted to two rounds of Delphi voting

Statement number	Statement	Level of agreement in round 1	Level of agreement in round 2	Outcome
4a	Due to differences in the origin and the production process, recombinant gonadotropins have a higher specific activity and lower response variability than urinary gonadotropins do	83%	85%	Consensus
4b*	Relative to urinary gonadotropins, recombinant gonadotropins yield one or two more oocytes	67%	96%	Consensus
4c	The addition of r-hLH to r-hFSH improves the outcomes in terms of the implantation rate and the ongoing pregnancy rate in women of advanced age (≥ 35)	79%	85%	Consensus

[*] Reformulated between rounds 1 and 2. See Supplementary Table 1

5c (79%) and 5e (62%) (see Supplementary Table 1 in the Online Resource).

The 26 experts were invited to participate in round 2, and all voted (Fig. 2). Of the 28 statements, eight achieved a full consensus, 16 achieved a consensus, and four did not achieve a consensus.

The pathophysiological role of LH in folliculogenesis

Overall, the seven statements in this section obtained the highest frequency of full agreement; most of the experts considered that the research evidence (sometimes based on experiments in non-human models) was more robust in this field than in clinical areas, which were more influenced by inter-individual variability (Table 1).

All seven statements concerning the pathophysiological role of LH in folliculogenesis achieved a consensus, including four with a full consensus. This high level of agreement was due to the experts' endorsement of the basic science and notably the two-cell, two-gonadotropin theory, whereby LH binds to cognate receptors on theca cells and thus stimulates the expression of the enzymes necessary for the production of androgens. The latter diffuse into granulosa cells, where they upregulate the expression of FSH receptors and are converted into oestrogens. Hence, the experts agreed that LH is required for normal or optimal folliculogenesis (statement 1a) because stimulation with FSH alone does not lead to the presence of a dominant follicle in all patients, and folliculogenesis can be impaired by LH receptor mutations [33, 34]. The two-cell, two-gonadotropin theory was cited as the basis of the need for a balance between LH and FSH (statement 1c), although the exact meaning of the words "harmonious" and "balance" in this context were questioned. Several FSH/LH ratios (2:1 but also < 1) were mentioned [35, 36].

Table 5 The subset of statements on the patient profile, as developed by the SAB and submitted to two rounds of Delphi voting

Statement number	Statement)	Level of agreement in round 1	Level of agreement in round 2	Outcome
5a	Patients with risk factors (such as a low body mass index, chronic disease, and advanced age) are more likely to need LH administration	96%	100%	Full consensus
5b	The POSEIDON classification of "low-prognosis" patients helps to guide treatment strategies	87%	92%	Consensus
5c*	A patient who presents a suboptimal follicular output rate (FORT) is a patient with a hyporesponse to ovarian stimulation	79%	88%	Consensus
5d	When follicular growth is inadequate, LH administration during stimulation is beneficial	58%	62%	No consensus
5e*	After an unexpectedly poor response to stimulation with r-hFSH, LH administration improves the ovarian response in patients with a relative LH deficiency	62%	96%	Consensus
5f	In women who are hyporesponders, LH administration from S1 onwards is needed to improve follicular recruitment	58%	77%	Consensus
5 g	In women with a low ovarian reserve, the ovarian response is optimized by LH administration	58%	62%	No consensus
5 h	In women who are poor responders, LH administration is associated with a higher live birth rate	50%	46%	No consensus
5i	Stimulation with a combination of r-hFSH + hMG does not improve the outcomes, compared with r-hFSH + r-hLH	58%	73%	Consensus

* Reformulated between rounds 1 and 2. See Supplementary Table 1

The experts also agreed that only a huge excess of LH (i.e. a supraphysiological level that would not be produced by current treatment protocols) would lead to the cessation of folliculogenesis (statement 1b) [37, 38]. The term "ceiling effect" was frequently quoted, as were clinical data on the deleterious effect of chronic LH elevation in polycystic ovary syndrome.

In contrast, the experts agreed that within its normal range, LH acts as a proliferative, anti-apoptotic factor in late folliculogenesis (statement 1 d) [34, 35, 39]. It should be noted that even though statement 1 d contained two sub-statements, a 100% consensus was achieved. The experts agreed that (as clearly acknowledged in the scientific literature) hCG has a longer half-life than LH (statement 1e) [39–44].

There was full consensus on the decrease in LH activity (but not necessarily in LH levels) with age, due to changes in glycosylation (statement 1f); again, a convergence between basic science and clinical observations was frequently cited [9, 45].

Lastly, there was full consensus on the existence and possible clinical impact of polymorphisms in LH and in the LH/hCG receptor (statement 1 g); again, assaying the concentration of LH alone was judged to be insufficient for judging the full clinical picture [9, 46–48].

LH administration for follicular development, prior to OI/IUI protocols

In line with their opinions on statement 1c (the need for balance between LH and FSH), experts fully agreed that the combined provision of FSH and LH in a 2:1 ratio is associated with optimal steroidogenesis and folliculogenesis for patients with hypogonadotropic hypogonadism (statement 2a) (Table 2) [49]. This ratio (as recommended by the European Recombinant Human LH Study Group) was judged to work well in clinical practice [50].

All but one of the experts agreed that the great majority of ovulating patients did not require LH administration for OI or IUI protocols (statement 2b). The only expert who disagreed suggested that irregular ovulation was common and hence questioned the accuracy of the term "great majority" used in the statement but otherwise was in line with the other opinions expressed.

Most of the experts agreed that in an IUI program, the relatively late introduction of a GnRH antagonist (with a short half-life) would not impact LH activity and hence would not prompt the need for LH administration (statement 2c) [51]. The four experts who moderately disagreed would have preferred slight changes in the wording, such as the addition of "with a normal hormone profile".

LH administration for follicular development, prior to IVF protocols

Most of the experts agreed that the long-term use of an oral contraceptive increased the likelihood of a hyporesponse in patients (statement 3a) (Table 3) [9]. Some experts chose to

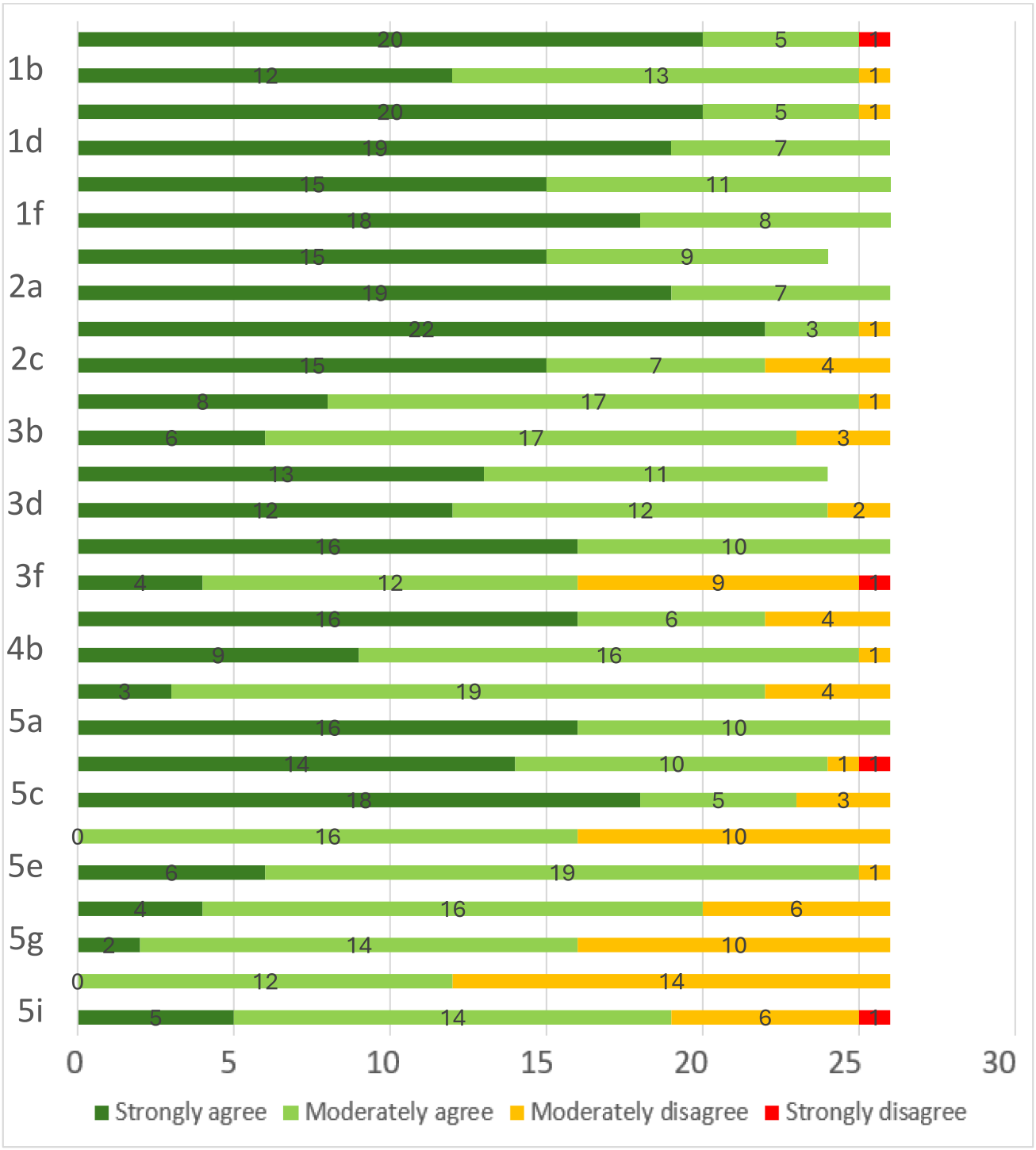

Fig. 2 The votes in round 2 of the Delphi survey

emphasize that (i) the longer the period of use, the greater the likelihood of a hyporesponse, and (ii) the oral contraceptive had a post-cessation carry-over effect that could last for several months; a minimum wash-out period of 5 days was mentioned [52]. Most of the experts emphasized the need to consider individual patient profiles (i.e. inter-individual variability) and the need to define "long-term" use precisely.

There was a consensus on the need for LH in long GnRH agonist protocols (statement 3b); however, the use of LH would depend on the magnitude and duration of LH

deficiency in women ovulating normally [53]. It was suggested that inhibition of the hypothalamus-pituitary axis did not necessarily lead to a LH deficiency and that even low residual LH levels were sufficient for folliculogenesis.

The statement (3c) whereby assaying the plasma LH concentration alone is not sufficient for determining whether or not LH administration is needed achieved a full consensus in the first round and was not included in the second round [9, 45]. The experts considered that in vivo LH activity did not reflect the concentration of LH determined in a laboratory assay, especially when considering LH pulsatility, inter-individual differences, intra-individual differences (i.e. changes over time in sensitivity), and analytical variability.

There was a consensus whereby the dissociation between hormone levels and ultrasound findings during ovarian stimulation is a sign of partial LH deficiency in patients with a normal ovarian reserve (statement 3d) [45, 54]. In general, the few experts who disagreed with statements about protocols cited a robust lack of clinical trial evidence.

In the second round, the experts reached a full consensus on the lack of a systematic need for LH in normal responders undergoing an antagonist protocol in the absence of pretreatment (statement 3e), in line with the European Society of Human Reproduction and Embryology's guidelines [53, 55–57]. In the first round, six experts cited factors other than the absence of pretreatment (i.e. the patient profile, irregular cycles, etc.).

No consensus was achieved on statement 3f (the effect of a combined oral contraceptive in an antagonist protocol vs. a long agonist protocol), due to a paucity of data, a blockade that was shorter for a combined oral contraceptive in an antagonist protocol than in a long agonist protocol, and the need to define the duration of contraceptive pretreatment [9].

The type and source of LH activity: urinary vs. recombinant gonadotropins

The experts considered that the biochemical characteristics of recombinant gonadotropins were clearly less variable than those of urinary gonadotropins, and so statement 4a achieved a consensus [58–61]. The need for more clinical trial evidence on differences in the ultimate endpoint (the live birth rate) was mentioned (Table 4).

Statement 4b (concerning a greater oocyte yield following treatment with recombinant gonadotropins) achieved a consensus, which was underpinned by Lehert et al.'s meta-analysis and by clinical trials comparing the originator follitropin alfa with highly purified urinary gonadotropins [62–66]. Some experts again pointed to the need for additional clinical trial data on the live birth rate.

Statement 4c (the advantages of adding r-hLH to recombinant human FSH (r-hFSH) for women over the age of 35) achieved a consensus, with broad agreement on the age-related decrease in LH activity mentioned in the "pathophysiology" section [16, 45]. Some experts highlighted the need for additional clinical trial data on factors other than age (such as inter-individual differences in responsiveness).

The need for LH administration as a function of the patient profile

All the experts agreed that patients with risk factors (such as a low body mass index, chronic disease, and advanced age) are more likely to require LH (statement 5a) [9]. The experts' recommendation of considering interindividual differences meant that the level of consensus was lower here than for the other topics.

The POSEIDON classification was approved as a guide to the best treatment approach (statement 5b): only three experts did not use it [67–69].

The follicular output rate (FORT) was widely acknowledged as a useful tool — but only one of several — for defining a patient with a hyporesponse to ovarian stimulation (statement 5c, after reformulation) [70, 71]. Full consensus was not achieved because some experts felt that the total number of oocytes was more important that the FORT or that a stimulation resulting in a hyporesponse had not been intense enough.

Statement 5d was close to achieving a consensus (62% agreement). Although some of the literature data suggested that LH administration during a stimulation cycle can be beneficial, some experts thought that it was preferable to initiate LH at the beginning of a subsequent cycle [22, 45, 54, 72].

A consensus was reached on statement 5e: LH administration after a poor response to r-hFSH was expected to be beneficial, while taking account of the nature and cause of any LH deficiency present [73, 74]. The value of early (rather than late) LH administration in hyporesponders (statement 5f) obtained a consensus [75]. A need for more clinical trial evidence in some subgroups was highlighted.

A marked proportion of the experts considered that LH and FSH co-treatment could improve the ovarian response in women with a low ovarian reserve, although statement 5g did not achieve a consensus [57, 67]. This was partly because the ESPART study had not demonstrated an advantage of r-hLH + r-hFSH over r-hFSH alone in terms of number of retrieved oocytes or the live birth rate when the poor ovarian response was not stratified as mild, moderate or severe [76]. Accordingly, statement 5h (focused on the live birth rate) failed to attract a consensus [8, 17, 57]. Lastly, there was a consensus on statement 5i: the action of hMG was not superior to that of r-hLH when each hormone was combined with r-hFSH [15, 77].

Discussion

The results of this two-round Delphi survey of a panel of experts offer clear, consistent guidance on clinical practice in France with regard to the use of LH in ovarian stimulation. The experts endorsed the basic science on LH and confirmed the hormone's critical role in the optimization of folliculogenesis. Recombinant human LH was validated for optimizing clinical outcomes in a range of patient profiles: a suboptimal ovarian response to IVF stimulation, desensitization following a long agonist protocol, advanced maternal age (> 35), polymorphisms, low body mass index, and women with hypogonadotropic hypogonadism.

It is noteworthy that the above-described consensus statements are in line with the recently reported results of a Delphi survey of 52 experts in France and Belgium on the management of key aspects of ovarian stimulation [31]. Notably, the experts agreed on the use of LH/hCG activity in cases of hypogonadotropic hypogonadism, advanced age, an inadequate response to initial stimulation, and suspected FSH receptor polymorphisms [31].

The present study differed in several respects from previous Delphi studies of this topic. At the time of our survey, only the Spanish Delphi study by Barrenetxea et al. had been published [20]. The study was much more general ("the use of gonadotrophins") with regard to ovarian stimulation: only four of the 35 statements concerned the combination of LH and FSH. Since then, other Delphi studies have been published. The Iranian Delphi study by Salehpour et al. focused on patient profiles, with some limited consideration of pathophysiological aspects and greater consideration of implantation [32]. Only 10 statements were initially considered. The Saudi Arabian Delphi study by Awwad et al. was also relatively general with regard to ovarian stimulation and focused on two specific patient profiles (advanced maternal age and hypo-responders) in which the additional use of LH might be beneficial [30]. There were no statements on the physiology of LH. The Belgian/French survey by Blockeel et al. was more general ("expert opinions on the management of key aspects of ovarian stimulation") and initially considered only 11 statements [31]. In comparison with these above-mentioned publications, our Delphi survey went back to basics and was much more exhaustive with regard to the pathophysiology of LH. It is noteworthy that despite interstudy differences in the profiles of the voting experts and in the national health systems, the various Delphi surveys' consensuses on LH converged.

Our study had a number of strengths. Firstly, in the absence of official guidelines, the present survey sought a consensus specifically on the use of LH in clinical practice. Secondly, the survey brought together experts in assisted reproduction from most of the main centres in France and thus is likely to be representative of current practice. Thirdly, statements were developed with regard to the international scientific literature and a broad spectrum of concerns (from basic science to real-life patient management), hence, the consensus statements may be applicable to other countries and healthcare systems.

The study also had a number of limitations — some of which are inherent to the frequently used Delphi method. Firstly, the procedure for selecting of panel members was not systematic and/or random; the panel members were selected (i.e. handpicked) on the basis of their expertise. Although this might have resulted in the inclusion of like-minded physicians, expertise-based handpicking was the method used in recent Delphi surveys of LH use [20, 30–32]. Secondly, voting in our survey was anonymous. On one hand, one could hypothesize that the anonymous, online voting constrained understanding. On the other, one could hypothesize that people with dissenting views felt freer to express themselves without being influenced or stigmatized. Thirdly, the experts who agreed to participate in the survey might have held stronger views than those who declined the invitation or did not reply; this might have resulted in selection bias. Fourthly, consensus was sometimes based on the clinical benefit observed by the experts, and large, randomized, controlled trials supporting some views were lacking — highlighting the need for further research in this area. Fifthly, we did not perform a thematic analysis of the experts' comments on the statements. Sixthly, we did not explore whether the consensus varied from one subgroup of experts to another (e.g. as a function of the public- vs. private-sector status of their host institution, for example). Seventhly, the statements discussed by the experts and presented here were first drafted in French and then translated into English. Slight variations in meaning cannot be ruled out. Lastly, the survey did not include any input from patients on (for example) the treatment burden and satisfaction with treatment; these topics would be relevant with regard to shared medical decision-making and might also be considered as relevant endpoints in future research.

Further clinical studies and especially real-world data on significant outcomes (e.g. the cumulative live birth rate) might enable the extrapolation of the current consensus to other patient subgroups (e.g. those with a low ovarian reserve, and those having received an agonist protocol). Furthermore, it is possible that along with clinical effectiveness, the cost-effectiveness of the formulations and protocols considered here will influence routine clinical decision-making. As mentioned above, patient-reported outcomes (e.g. perception of the treatment burden and the level of satisfaction with treatment) might be relevant supporting endpoints in future clinical studies. Lastly, it would be interesting to analyze narrower age classes in

Poseidon groups 3 and 4 because the outcomes might be better in women aged 35–39 than in women aged ≥ 40.

In conclusion, and given the importance of time in each patient's journey, it is crucial to rapidly identify individuals who can benefit from LH administration. Choosing the right treatment quickly is essential because the drop-out rate after the first cycle can be as high as 65% [8, 78–80]. This type of guidance from clinicians on ART strategies in France could complement guidelines and policies, and may help to further improve treatment outcomes.

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Data availability The data that support the findings of this study are not openly available due to reasons of sensitivity but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This opinion survey did not encompass any patient data or experiments on human participants. Under the terms of the French legislation, the study did not require ethical approval.

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