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RESEARCH ARTICLE

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Use of gonadotropins in ovarian stimulation in Spain: Delphi consensus

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ABSTRACT

Two-round Delphi study carried out in Spain. Three theme-based blocks were set out: 1) Patient profiles: therapeutic goal and parameters to be analysed according to POSEIDON patient profiles; 2) Ovarian stimulation protocols with antagonists: monotherapy (FSH) vs combined therapy (FSH + LH/HMG); 3) Safety and effectiveness of the devices. The antral follicle count and the anti-Müllerian hormone level were considered indicators that can be used to predict ovarian response. More than 80% of the participants agreed that FSH monotherapy is the recommended regimen in normal/hyper-responsive patients of < 35 years of age; that 150–300 IU is the dose to be used in ovarian stimulation in monotherapy depending on clinical parameters; and that FSH monotherapy improves patients' comfort compared to two combined drugs. It was unanimously considered that the type of device used by the patient influences the comfort of the treatment.

IMPACT STATEMENT

- **What is already known on this subject?** There is currently no consensus on the optimal treatment for controlled ovarian stimulation for patients undergoing IVF which leads to highly variable clinical practices.
- **What the results of this study add?** This study's strong point is that, since it is a consensus, it has been possible to include more topics than would normally be dealt with in a systematic review or guidelines, which are generally based on a strict method that restricts the scope of the research. Experts have reached a consensus on most of the statements and based on these they have issued consensus statements that will enable the optimal use of gonadotropins in IVF.
- **What the implications are of these findings for clinical practice and/or further research?** This Delphi consensus provides a real-life clinical perspective on gonadotropin usage in IVF.

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KEYWORDS
Ovarian stimulation; in vitro fertilisation; poor responder; FSH

Introduction

Ovarian stimulation is crucial in each cycle of in vitro fertilisation (IVF) because the development of a sufficient number of follicles and attainment of a sufficient number of oocytes increases not only the live birth rate per cycle but also the cumulative live birth rate per cycle of treatment (Drakopoulos *et al.* 2016; Siristatidis, 2013).

Ovarian stimulation faces different challenges. On the one hand, the live birth rate per mature oocyte retrieved is lower than 5% (Goldman *et al.* 2013). On the other, the number of oocytes necessary to obtain at least one live birth increases exponentially with age (Goldman *et al.* 2017). Furthermore, a significant number of patients (from 9% to 24%) show a poor ovarian response (POR) to stimulation with exogenous gonadotropins (Roque *et al.* 2021). As a result, low rates of pregnancy and live births are obtained, both varying from 3% to 14% (Drakopoulos *et al.* 2016; Humaidan *et al.* 2017; La Marca *et al.* 2016; Tarlatzis *et al.* 2003; Ulug *et al.* 2003).

In order to predict the clinical response to stimulation and choose the most appropriate protocol, patients should be stratified according to ovarian reserve markers (La Marca *et al.* 2016). However, the choice of a marker is controversial and there is still debate as to what marker (or combination of them) is the most suitable (Bulletti *et al.* 2021).

The POSEIDON criteria stratify patients into four groups depending on a combination of quantitative and qualitative parameters (Alviggi *et al.* 2016). They are based on the woman's age, ovarian reserve biomarkers, ovarian sensitivity to exogenous gonadotropins, and the number of oocytes retrieved in an IVF cycle (Alviggi *et al.* 2016).

The 'ideal' approach to performing ovarian stimulation with POR patients is still not known in terms of medication type, dose and devices used (Bulletti *et al.* 2021). There is no

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single procedure that appears to clearly improve IVF outcomes for this subgroup of patients, and clinical trials are generally highly biased (Papathanasiou, *et al*. 2016). Various ovarian stimulation protocols have been put forward that use exogenous FSH combined with gonadotropin-releasing hormone (GnRH) analogues (Bulletti *et al*. 2021). Another point of discrepancy is whether to use a combined treatment of FSH with luteinising hormone (LH), hormones with an LH effect, or else monotherapy with FSH (Ferrando *et al*. 2020).

It can be concluded that there is currently no consensus on the optimal treatment for controlled ovarian stimulation for POR patients undergoing IVF (Olgan and Humaidan 2017; Pandian *et al*. 2010; Papathanasiou, *et al*. 2016), which leads to highly variable clinical practices.

Given this background, this study took up the following goals: 1) To identify the points of agreement or disagreement as regards the use of gonadotropins in IVF in Spain; and 2) To issue recommendations to optimise the use of gonadotropins in IVF, both conventionally and using IVF-ICSI.

Method

Scientific committee and panel of experts

This project was carried out using the Delphi method from March to December 2021 in Spain. Initially, an advisory committee was set up tasked with analysing the main controversies in the sphere of ovarian stimulation in IVF, drawing up a questionnaire, interpreting the results from the Delphi rounds and critically reviewing the final report.

The committee members were chosen based on the following: they should be specialists and spend most of their working days in IVF sites (public or private); belong to a scientific society in this field; and be authors of publications or communications or have participated in clinical trials in the sphere of IVF.

In order to answer the questionnaire, a panel of experts was created with 40 fertility specialists from public and private sites with extensive experience in IVF and from all regions in the country.

As this study was based on a Delphi survey ethics approval was not required.

Creating statements. Questionnaire

The advisory committee first identified the areas of uncertainty that should form the basis for the questionnaire's structure. Three theme-based blocks were set out: 1) Patient profiles: therapeutic goal and parameters to be analysed based on POSEIDON patient profiles; 2) Ovarian stimulation protocols: monotherapy (FSH) vs combined therapy (FSH + LH/HMG); 3) Safety and effectiveness of the devices.

Each member of the committee proposed different statements for the questionnaire with their corresponding bibliographic basis. To do so, the guidelines, protocols and other available evidence were reviewed, putting them into context with each committee member's clinical experience. A work meeting was held to pool all of the statements and validate the choices. The final questionnaire contained 33 statements divided into five blocks or sub-blocks. It was posted on a microsite that the participants accessed via a web link with a user password.

Statistical analysis and interpretation of results

Two Delphi rounds were carried out. In each of them, the panel of participants scored each statement on a 9-point Likert scale. The level of agreement was classified as 1–3 (disagree), 4–6 (neither agree nor disagree), or 7–9 (agree).

The mean values (standard deviation) were calculated, as well as the median and interquartile range (p25–p75) for each of the questionnaire's items. The level of significance was measured with the Kolmogorov-Smirnov goodness-of-fit test for distribution.

The criteria for consensus included 'unanimity' when 100% of participants agreed on the same Likert scale category, 'consensus' when there was agreement among $\geq$ 80% of participants, 'majority' when there was agreement among $\geq$ 66% of participants, and 'disagreement' when there was agreement among $<$ 66% of the participants. For the purposes of this analysis, the 'unanimity', 'majority' and 'consensus' groups were considered all together as consensus.

After the first round, the questions that did not reach a consensus in replies went on to the second, reformulating the ones whose wording could be improved. When the statistical analysis of the results was available, the advisory committee met to discuss and define the conclusions from the study.

The initial questionnaire contained 33 statements divided among the three aforementioned blocks (with 16, 14 and 3 statements respectively).

- Patient profiles
  a. Parameters to stratify patients with a low ovarian response: 9 statements
  b. Goals of the ovarian stimulation treatment: 7 statements
- Ovarian stimulation protocols: monotherapy (rFSH) vs. combined therapy (rFSH + LH/HMG) with antagonists
  a. Monotherapy: 10 statements
  b. Combined therapy: 4 statements
- Safety/efficiency of the device: 3 statements

Results

The questionnaire was answered by 40 fertility specialists. The participating entities are listed in Table 1.

Figure 1 shows the process of Delphi rounds. In the first round, a consensus was reached for 27 of the 33 matters raised. Of the six remaining questions, one was eliminated after being reviewed by the committee and considering that consensus would not be reached, while the rest went on to the second round, having been reformulated to make them more understandable, so that the final results included 32 statements.

Table 2 shows the results from the Delphi study.

Table 1. Participating sites.

Autonomous Community region	Province	Site
Andalusia	Cádiz	Puerta del Mar University Hospital
	Córdoba	Reina Sofía University Hospital
	Granada	Virgen de las Nieves University Hospital
	Málaga	Gutenberg Centre
	Huelva	Juan Ramón Jiménez University Hospital
	Jaén	Jaén University Hospital
	Seville	Virgen del Rocío University Hospital
	Seville	IVI Clinic – Seville
Aragon	Zaragoza	Montpellier Reproduction Unit
Canaries	Santa Cruz, Tenerife	Canary Islands University Hospital
	Las Palmas	Canary Islands University Hospital
Cantabria	Santander	Marquis de Valdecilla University Hospital
Castile - La Mancha	Albacete	Bernabéu Institute
Castile and Leon	Valladolid	Valladolid Clinical University Hospital
Catalonia	Barcelona	CIRH
	Barcelona	Eugin Clinic
	Barcelona	Ginefiv - Barcelona
	Barcelona	Clinical University Hospital Barcelona
	Barcelona	Santa Creu i Sant Pau Hospital
	Barcelona	IVI - Barcelona
	Barcelona	Quirón Salud Hospital Barcelona
	Tarragona	Embryogyn
Madrid Community	Madrid	IVI Clinic - Madrid
	Madrid	Ginefiv - Madrid
	Madrid	San Carlos Clinical Hospital
	Madrid	Gregorio Marañón University Hospital
	Madrid	Bernabéu Institute
	Madrid	IVF Life
Chartered Community of Navarre	Pamplona	Assisted Reproduction Institute, Quirón Salud Pamplona
Valencia Community region	Alicante	UR Vistahermosa
	Valencia	IVI Clinic - Valencia
Extremadura	Badajoz	CERHA Extremadura Centre for Assisted Human Reproduction
Galicia	Pontevedra	IVI Clinic - Vigo
Balearic Islands	Majorca	Son Espases University Hospital - Reproduction Unit
	Majorca	Bernabéu Institute
	Majorca	IVI Clinic - Majorca
Basque Country	Guipuzkoa	Donostia University Hospital
	Biscay	Cruces University Hospital
Murcia	Murcia	IVI Clinic – Murcia
	Murcia	Virgen de la Arrixaca University Clinical Hospital

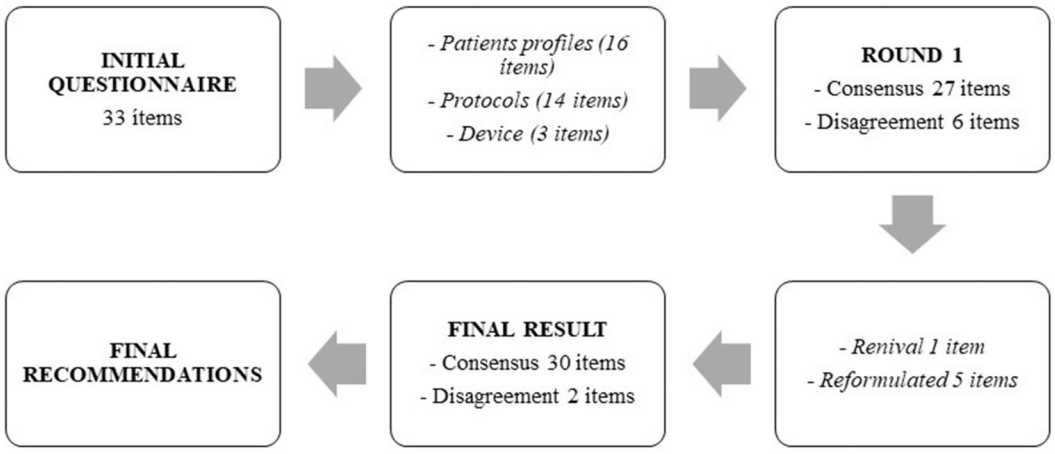

Figure 1. Delphi study flow chart.

Discussion

This Delphi consensus provides a real-life clinical perspective on gonadotropin usage in IVF. The experts reached a consensus on most of the statements and based on these they have issued recommendations (Table 3) that will enable optimal use of gonadotropins in IVF, whether conventionally or as IVF-ICSI.

As regards the parameters for stratifying patients with low ovarian response, initially there are different parameters available to stratify the patients, such as age, baseline follicle-stimulating hormone (FSH) concentration, anti-Müllerian hormone (AMH) concentration, and the antral follicle count (AFC), used alone or in combination via algorithms or clinical nomograms. Despite this, the choice of marker is

Table 2. Final results from the Delphi study. Statements that did not reach consensus by the end of the study are marked in italics.

ITEM		MEDIUM RANGE	PARTICIPANTS WITHIN RANGE OF AGREEMENT (7–9)	PARTICIPANTS IN AN INDIFFERENT RANGE (4–6)	PARTICIPANTS WITHIN RANGE OF DISAGREEMENT (7–9)	CONSENSUS
PARAMETERS TO STRATIFY PATIENTS WITH A LOW OVARIAN RESPONSE						
Q01a	The baseline indicator for designing an ovarian stimulation protocol is the patient's age.	7–9	26 (65%)	10 (25%)	4 (10%)	Discrepancy
Q01b	The ovarian stimulation protocol must be designed taking into account the patient's age.	7–9	39 (97.5%)	1 (2.5%)	0 (0%)	Consensus
Q02	The result from the previous cycles carried out by the patient is fundamental in designing a new ovarian stimulation protocol.	7–9	39 (97.5%)	1 (2.5%)	0 (0%)	Consensus
Q03	In patients with previous stimulation cycles, the most important indicators to take into account on designing the ovarian stimulation protocol are the doses of gonadotropins used and the number of oocytes retrieved.	7–9	37 (92.5%)	2 (5%)	1 (2.5%)	Consensus
Q04	For patients with no previous cycles, the indicators to be considered on designing the ovarian stimulation protocol are the antral follicle count, anti-Müllerian hormone, age and body mass index.	7–9	40 (100%)	0 (0%)	0 (0%)	Unanimity
Q05	The indicators that can be used to predict ovarian response are the antral follicle count and the anti-Müllerian hormone value.	7–9	39 (97.5%)	1 (2.5%)	0 (0%)	Consensus
Q06a	Age alone is not a good predictor ovarian response.	7–9	26 (65%)	9 (22.5%)	5 (12.5%)	Discrepancy
Q06b	*Age alone is not a good quantitative predictor of ovarian response.*	*7–9*	*26 (65%)*	*10 (25%)*	*4 (10%)*	Discrepancy
Q07	The antral follicle count evaluation is a clinical practice recommended for all patients prior to stimulation, in each cycle.	7–9	39 (97.5%)	1 (2.5%)	0 (0%)	Consensus
Q08	Anti-Müllerian hormone testing is a recommended practice in all patients before the first cycle of treatment and if the patient's clinical conditions vary.	7–9	34(85%)	5 (12.5%)	1 (2.5%)	Consensus
Q09	Body mass index is a recommended measurement parameter for all patients.	7–9	37 (92.5%)	3 (7.5%)	0 (0%)	
GOALS OF OVARIAN STIMULATION TREATMENT						
Q10	The appropriate number of oocytes that should be obtained in an ovarian stimulation cycle may vary depending on the patient's age and clinical profile.	7–9	35 (87.5%)	3 (7.5%)	2 (5%)	Consensus
Q11	The main determining factors to achieve an adequate number of oocytes during ovarian stimulation are age and the number of antral follicles at the start of stimulation.	7–9	31 (77.5%)	8 (20%)	1 (2.5%)	Consensus
Q12	The goal of ovarian stimulation for patients with a diagnosis of low reserve is to obtain the maximum possible amount of oocytes compared to the number of antral follicles available before beginning stimulation.	7–9	40 (100%)	0 (0%)	0 (0%)	Unanimity
Q13	The goal of ovarian stimulation for normal-responding patients could be set at obtaining 10–15 oocytes.	7–9	36 (90%)	1 (2.5%)	3 (7.5%)	Consensus
Q14	For normal-responding patients, the optimum range of response is considered to be 9 or more oocytes.	7–9	38 (95%)	1 (2.5%)	1 (2.5%)	Consensus
Q15	Ovarian stimulation of more than 20 oocytes increases the risk of complications.	7–9	36 (90%)	3 (7.5%)	1 (2.5%)	Consensus
Q16	The increased risk of complications influences the number of oocytes to be obtained in an ovarian stimulation cycle in patients. The number of oocytes to be obtained must therefore be weighed against the risk of hyper-stimulation and the risk of haemoperitoneum.	7–9	33 (82.5%)	7 (17.5%)	0 (0%)	Consensus

(*continued*)

Table 2. Continued.

ITEM		MEDIUM RANGE	PARTICIPANTS WITHIN RANGE OF AGREEMENT (7–9)	PARTICIPANTS IN AN INDIFFERENT RANGE (4–6)	PARTICIPANTS WITHIN RANGE OF DISAGREEMENT (7–9)	CONSENSUS
OVARIAN STIMULATION PROTOCOLS: MONOTHERAPY (FSHr)						
Q17	FSH monotherapy is the regimen commonly recommended for normal- or hyper-responding patients under 35 years of age.	7–9	38 (95%)	1 (2.5%)	1 (2.5%)	Consensus
Q18	The dose used in ovarian stimulation in monotherapy is from 150 to 300 IU depending on the clinical parameters defined at the start of stimulation.	7–9	39 (97.5%)	1 (2.5%)	0 (0%)	Consensus
Q19	In the event of a low previous response or low ovarian reserve, a dose of 300 IU is the most common.	7–9	32 (80%)	4 (10%)	4 (10%)	Consensus
Q20a	For hyper-responsive patients, the starting dose for FSH is usually 75 to 100 IU.	4–6	10 (25%)	11 (27,5%)	19 (47,5%)	Discrepancy
Q20b	For hyper-responsive patients, the starting dose for FSH is usually 75 to 150 IU.	7–9	32 (80%)	5 (12.5%)	3 (7.5%)	Consensus
Q21a	For patients with polycystic ovaries, the starting dose of FSH is usually 75 to 100 IU.	4-6	9 (22,5%)	12 (20%)	19 (47,5%)	Discrepancy
Q21b	For patients with polycystic ovaries, the starting dose of FSH is usually 75 to 150 IU.	7–9	30 (75%)	5 (12.5%)	5 (12.5%)	Consensus
Q22	FSH in monotherapy increases the patient's comfort compared to using two different drugs in combination.	7–9	33 (82.5%)	5 (12.5%)	2 (5%)	Consensus
Q23a	*FSH in monotherapy increases adherence to treatment compared to the use of two different drugs combined.*	*4-6*	*16 (40%)*	*14 (35%)*	*10 (25%)*	*Discrepancy*
Q24	FSH in monotherapy reduces mistakes in handling the medication.	7–9	30 (75%)	8 (20%)	2 (5%)	Consensus
Q25	Stimulation can begin between day 2 and day 4, giving greater flexibility for the first monitoring	7–9	33 (82.5%)	4 (10%)	3 (7.7%)	Consensus
Q26a	Changes or variations in the dose used during ovarian stimulation gives no advantage in the final outcome	7–9	24 (60%)	6 (15%)	10 (25%)	Discrepancy
Q26b	There is no evidence that changes or variations in the dose used after ovarian stimulation has begun gives advantages in the final outcome.	7–9	29 (72.5%)	4 (10%)	7 (17.5%)	Consensus
OVARIAN STIMULATION PROTOCOLS: MONOTHERAPY (rFSH) VS. COMBINED THERAPY (rFSH + LH/HMG) WITH ANTAGONISTS						
Q27	Combined ovarian stimulation treatment is only indicated for certain groups of patients.	7–9	29 (72.5%)	4 (10%)	7 (17.5%)	Consensus
Q28	The most common indications for receiving ovarian stimulation treatment combined with LH are an age of over 35 years and poor response in previous cycles.	7–9	35 (87.5%)	5 (12.5%)	0 (0%)	Consensus
Q29	It was unanimously accepted that other indications for adding LH-acting drugs are excessive pituitary LH suppression or a lack of response to FSH alone in previous cycles.	7–9	40 (100%)	0 (0%)	0 (0%)	Unanimity
Q30	Generally, normal-responding patients under 35 years of age do not benefit from ovarian stimulation treatment combined with drugs with a LH effect.	7–9	29 (72.5%)	11 (27.5%)	0 (0%)	Consensus
SAFETY/EFFICIENCY OF THE DEVICE						
Q31	The type of device used by the patient influences the safety of ovarian stimulation treatment.	7–9	30 (75%)	7 (17.5%)	3 (7.5%)	Consensus
Q32	The type of device used by the patient influences the comfort of ovarian stimulation treatment.	7–9	40 (100%)	0 (0%)	0 (0%)	Unanimity
Q33	The device used must ensure as much as possible that the dose selected is the one administered by the patient.	7–9	38 (95%)	2 (5%)	0 (0%)	Consensus

FSH: follicle-stimulating hormone; LH: luteinising hormone. a: Statements that did not reach consensus in first round; b: statements revised for 2° round
*statement eliminated.

Table 3. Recommendations to optimise the use of gonadotropins in IVF, both conventionally and in IVF-ICSI.

Stratification of patients with a low ovarian response
- The ovarian stimulation protocol must be designed taking into account the patient's age.
- The result from the previous cycles carried out by the patient is fundamental in designing a new ovarian stimulation protocol.
- For patients with previous stimulation cycles, the most important indicators to take into account on designing the ovarian stimulation protocol are the doses of gonadotropins used and the number of oocytes retrieved.
- For patients with no previous cycles, the indicators to be considered on designing the ovarian stimulation protocol are the antral follicle count, anti-Müllerian hormone, age and body mass index.
- The indicators that can be used to predict ovarian response are the antral follicle count and the anti-Müllerian hormone value.
- The antral follicle count evaluation is a clinical practice recommended for all patients prior to stimulation, in each cycle.

Ovarian stimulation protocols: monotherapy (rFSH)
- FSH monotherapy is the regimen commonly recommended for normal- or hyper-responding patients under 35 years of age.
- The dose used in ovarian stimulation in monotherapy is from 150 to 300 IU depending on the clinical parameters defined at the start of stimulation.
- In the event of a low previous response or low ovarian reserve, a dose of 300 IU is the most common.
- For hyper-responsive patients, the starting dose for FSH is usually 75 to 150 IU.
- For patients with polycystic ovaries, the starting dose of FSH is usually 75 to 150 IU.
- FSH in monotherapy increases the patient's comfort compared to using two different drugs in combination.
- FSH in monotherapy reduces mistakes in handling the medication.
- Stimulation can begin between day 2 and day 4, giving greater flexibility for the first control.
- There is no evidence that changes or variations in the dose used after ovarian stimulation has begun gives advantages in the final outcome.

Ovarian stimulation protocols: monotherapy (rFSH) vs. combined therapy (rFSH + LH/HMG) with antagonists
- Combined ovarian stimulation treatment is only indicated for certain groups of patients.
- The most common indications for receiving ovarian stimulation treatment combined with LH are an age of over 35 years and poor response in previous cycles.
- Other indications for adding LH-acting drugs are excessive pituitary LH suppression or a lack of response to FSH alone in previous cycles.
- Generally, normal-responding patients under 35 years of age do not benefit from ovarian stimulation treatment combined with drugs with a LH effect.

Safety/efficiency of the device
- The type of device used by the patient influences the safety of ovarian stimulation treatment.
- The type of device used by the patient influences the comfort of ovarian stimulation treatment.

controversial and there is still debate as to what marker (or combination of them) is the most suitable (Bulletti *et al.* 2021).

Although other authors have described baseline FSH, body mass index and older age as predictors of ovarian response, the experts considered antral follicle count and the AMH value to be predictors of response, which are also indicators that are preferentially recommended by the guidelines of the European Society of Human Reproduction and Embryology (Bosch *et al*. 2020) compared to other markers. The participants agreed on recommending antral follicle counts for all patients before stimulation and in each cycle. The experts also consider that when a previous cycle is available, an antral follicle count or a determination of AMH should be carried out, but that it is unnecessary to measure the basal FSH.

Other authors have described factors such as baseline FSH, BMI, age or the number of follicles smaller than 11 mm as the most conclusive variables for patients under 35 years of age treated with recombinant FSH (rFHS) monotherapy (Howles *et al*. 2006).

As for the goals of treatment for ovarian stimulation, there was agreement of greater than 80% that the goal of ovarian stimulation for normal-responding patients could be set at obtaining 10–15 oocytes. There was also consensus that the adequate number of oocytes to be obtained in a cycle may vary depending on the patient's age and clinical profile, with a higher risk of complications if the result is greater than 20 oocytes; and that the increase in this risk determines the number of oocytes to be obtained in an ovarian stimulation cycle. In this vein, a recent Delphi study by Bulletti *et al* has revealed a broad consensus on assertions such as the goal of 8–14 oocytes retrieved after ovarian stimulation in fresh cycles (Bulletti *et al.* 2021). According to data from the National Registry of the Spanish Fertility Society (SEF) for 2019 (Sociedad Española de Fertilidad, 2019), the estimated number of oocytes necessary to achieve pregnancy was 14.3, and the number of inseminated or injected oocytes necessary to achieve pregnancy was 11.3 (in both fresh and cryopreserved transfers) (Sociedad Española de Fertilidad, 2019).

In terms of the ovarian stimulation protocols, a consensus was achieved in all of the items in this block. The experts agreed that the most usual indications for receiving ovarian stimulation treatment combined with LH are an age of over 35 years and poor response in previous cycles, although the scientific evidence is controversial, to say the least. It was unanimously accepted that other indications for adding LH-acting drugs are excessive pituitary LH suppression or a lack of response to FSH alone in previous cycles.

As regards ovarian stimulation, there is no single intervention that clearly improves IVF outcomes for patients with poor ovarian response. In general, clinical trials give controversial results (Papathanasiou *et al*. 2016). In a systematic review of 75 clinical trials carried out with POR patients over 15 years, there was a notable heterogeneity detected in defining this type of patient and in the interventions studied, as well as serious methodological problems (Papathanasiou *et al*. 2016). Only 10% of the trials reported a significant improvement in reproductive outcomes after applying different protocols, many of which were based on a single clinical trial (Papathanasiou *et al*. 2016).

Although there are guidelines on ovarian stimulation in IVF-ICSI published in 2019 by the ESHRE (Bosch *et al.* 2020), they are limited by the fact that only a small proportion of patients are included in randomised controlled trials; it is estimated that only 35% of POR patients would meet the inclusion criteria used in large clinical trials (Orvieto *et al*. 2021). Thus, prospective studies with an adequate sample size and

statistical power are still needed to respond to the clinical questions raised about ovarian stimulation for these patients.

Some authors have put forward different protocols using exogenous FSH combined with gonadotropin-releasing hormone (GnRH) analogues, whether agonist or antagonist (Bulletti *et al.* 2021). On the one hand, proper individualisation of the FSH dose has been put forward as one of the most sensitive steps to give a successful outcome and reduce complications from IVF (Bulletti *et al.* 2021). On the other, fixed-dose gonadotropin stimulation regimens (as opposed to variable doses during stimulation) have been considered a suitable option for some patients due to their lower cost and greater comfort, with fewer follow-up visits compared to the protocol with variable doses of gonadotropins (Bulletti *et al.* 2021). Another point of discrepancy is whether to use monotherapy wit FSH or else combine FSH with luteinising hormone (LH) or hormones with an LH effect (Ferrando *et al.* 2020). The scarcity of scientific evidence and the variability in clinical practice have prompted several Delphi studies to seek consensus (Bulletti *et al.* 2021; Orvieto *et al.* 2021).

The clinical effectiveness of rFSH monotherapy has been demonstrated in both clinical trials and real-life studies (Ferrando *et al.* 2020; Selman and Rinaldi 2016; Vlaisavljević *et al.* 2010; Strowitzki *et al.* 2016). In one of them, carried out in Spain with 1,222 patients treated in 26 sites, the pregnancy rates varied from 23.2% in poor responders to 37% in normal-responders (Ferrando *et al.* 2020).

The range of rFSH doses chosen by experts for ovarian stimulation protocols generally coincides with the range published in the ESHRE guide, which recommends doses ranging from 150 IU for good responders to 300 IU for poor responders (Bosch *et al.* 2020).

The results obtained in terms of safety and efficiency of the device agree with various studies comparing devices used in ovarian stimulation. However, these show differences in the reduction of handling errors (Imthurn *et al.* 2014; Saunders *et al.* 2020), comfort of use (Quintero *et al.* 2016) and the patient's preference (Quintero *et al.* 2016).

This study's strong point is that, since it is a consensus, it has been possible to include more topics than would normally be dealt with in a systematic review or guidelines, which are generally based on a strict method that restricts the scope of the research. Nevertheless, the consensus also has its limitations. For example, not all of the statements reached 100% agreement. Furthermore, although these recommendations represent experts' points of view, they are not universal. The patient's individual characteristics should always be taken into account before choosing the type of treatment.

We trust that this analysis will provide a contribution in improving care and therapeutic outcomes for POR patients undergoing IVF.

Conclusions

This Delphi study gives relevant data regarding the clinical reality of ovarian stimulation for POR patients undergoing IVF in Spain: 1) The different gonadotropins cannot alter the quality of the oocytes obtained; 2) The goal of ovarian stimulation is to obtain an adequate number of oocytes (in poor responders this is the maximum number possible, and in normal- or hyper-responders it is between 10 and 15); 3) The starting dose is determined well by response prediction factors; 4) The most valid prediction factor is the response in a previous cycle; 5) If there is no previous cycle, the antral follicle count and AMH value are the most reliable indicators of response.

This practical perspective is of great value in a field with numerous clinical questions raised and a high variability in clinical practice due to the scarcity of conclusive scientific evidence.

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