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ESHRE PAGES

ESHRE guideline: ovarian stimulation for IVF/ICSI†

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STUDY QUESTION: What is the recommended management of ovarian stimulation, based on the best available evidence in the literature?

SUMMARY ANSWER: The guideline development group formulated 84 recommendations answering 18 key questions on ovarian stimulation.

WHAT IS KNOWN ALREADY: Ovarian stimulation for IVF/ICSI has been discussed briefly in the National Institute for Health and Care Excellence guideline on fertility problems, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologist has published a statement on ovarian stimulation in assisted reproduction. There are, to our knowledge, no evidence-based guidelines dedicated to the process of ovarian stimulation.

STUDY DESIGN, SIZE, DURATION: The guideline was developed according to the structured methodology for development of ESHRE guidelines. After formulation of key questions by a group of experts, literature searches and assessments were performed. Papers published up to 8 November 2018 and written in English were included. The critical outcomes for this guideline were efficacy in terms of cumulative live birth rate per started cycle or live birth rate per started cycle, as well as safety in terms of the rate of occurrence of moderate and/or severe ovarian hyperstimulation syndrome (OHSS).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Based on the collected evidence, recommendations were formulated and discussed until consensus was reached within the guideline group. A stakeholder review was organized after finalization of the draft. The final version was approved by the guideline group and the ESHRE Executive Committee.

MAIN RESULTS AND THE ROLE OF CHANCE: The guideline provides 84 recommendations: 7 recommendations on pre-stimulation management, 40 recommendations on LH suppression and gonadotrophin stimulation, 11 recommendations on monitoring during ovarian stimulation, 18 recommendations on triggering of final oocyte maturation and luteal support and 8 recommendations on the prevention of OHSS. These include 61 evidence-based recommendations—of which only 21 were formulated as strong recommendations—and 19

good practice points and 4 research-only recommendations. The guideline includes a strong recommendation for the use of either antral follicle count or anti-Müllerian hormone (instead of other ovarian reserve tests) to predict high and poor response to ovarian stimulation. The guideline also includes a strong recommendation for the use of the GnRH antagonist protocol over the GnRH agonist protocols in the general IVF/ICSI population, based on the comparable efficacy and higher safety. For predicted poor responders, GnRH antagonists and GnRH agonists are equally recommended. With regards to hormone pre-treatment and other adjuvant treatments (metformin, growth hormone (GH), testosterone, dehydroepiandrosterone, aspirin and sildenafil), the guideline group concluded that none are recommended for increasing efficacy or safety.

LIMITATIONS, REASON FOR CAUTION: Several newer interventions are not well studied yet. For most of these interventions, a recommendation against the intervention or a research-only recommendation was formulated based on insufficient evidence. Future studies may require these recommendations to be revised.

WIDER IMPLICATIONS OF THE FINDINGS: The guideline provides clinicians with clear advice on best practice in ovarian stimulation, based on the best evidence available. In addition, a list of research recommendations is provided to promote further studies in ovarian stimulation.

STUDY FUNDING/COMPETING INTEREST(S): The guideline was developed and funded by ESHRE, covering expenses associated with the guideline meetings, with the literature searches and with the dissemination of the guideline. The guideline group members did not receive payment. F.B. reports research grant from Ferring and consulting fees from Merck, Ferring, Gedeon Richter and speaker's fees from Merck. N.P. reports research grants from Ferring, MSD, Roche Diagnositics, Theramex and Besins Healthcare; consulting fees from MSD, Ferring and IBSA; and speaker's fees from Ferring, MSD, Merck Serono, IBSA, Theramex, Besins Healthcare, Gedeon Richter and Roche Diagnostics. A.L.M reports research grants from Ferring, MSD, IBSA, Merck Serono, Gedeon Richter and TEVA and consulting fees from Roche, Beckman-Coulter. G.G. reports consulting fees from MSD, Ferring, Merck Serono, IBSA, Finox, Theramex, Gedeon-Richter, Glycotope, Abbott, Vitrolife, Biosilu, ReprodWissen, Obseva and PregLem and speaker's fees from MSD, Ferring, Merck Serono, IBSA, Finox, TEVA, Gedeon Richter, Glycotope, Abbott, Vitrolife and Biosilu. E.B. reports research grants from Gedeon Richter; consulting and speaker's fees from MSD, Ferring, Abbot, Gedeon Richter, Merck Serono, Roche Diagnostics and IBSA; and ownership interest from IVI-RMS Valencia. P.H. reports research grants from Gedeon Richter, Merck, IBSA and Ferring and speaker's fees from MSD, IBSA, Merck and Gedeon Richter. J.U. reports speaker's fees from IBSA and Ferring. N.M. reports research grants from MSD, Merck and IBSA; consulting fees from MSD, Merck, IBSA and Ferring and speaker's fees from MSD, Merck, IBSA, Gedeon Richter and Theramex. M.G. reports speaker's fees from Merck Serono, Ferring, Gedeon Richter and MSD. S.K.S. reports speaker's fees from Merck, MSD, Ferring and Pharmasure. E.K. reports speaker's fees from Merck Serono, Angellini Pharma and MSD. M.K. reports speaker's fees from Ferring. T.T. reports speaker's fees from Merck, MSD and MLD. The other authors report no conflicts of interest.

Key words: ovarian stimulation / ESHRE / guideline / evidence based / treatment / GRADE / poor responder / high responder / ovarian hyperstimulation syndrome

WHAT DOES THIS MEAN FOR PATIENTS?

Ovarian stimulation is an important first step in many fertility treatments. During ovarian stimulation, doctors prescribe different medications that stimulate the ovaries into producing 5 to 10 mature eggs, instead of one egg in a normal menstrual cycle. These eggs are then removed from the ovaries during egg pickup and later fertilized with sperm in the lab. The resulting fertilized eggs (now embryos) are transferred to the women's womb resulting in a pregnancy, if all goes well.

There are several options for ovarian stimulation, but they all include a series of different medications taken over several days/weeks, called a stimulation protocol. There is no one treatment scheme that works for each woman undergoing fertility treatment. Some patients may develop only very few eggs (and the stimulation will have to be repeated), while others may over-react with a risk of a serious complication (called ovarian hyperstimulation syndrome).

The current guideline aims to give advice to fertility doctors on which stimulation protocols are safe and effective. The guideline further provides advice on whether clinicians can predict how patients will react and how to adapt the stimulation protocol, for example for patients expected to be at risk of ovarian hyperstimulation syndrome. Finally, there is some advice on 'add-on' treatments (growth hormone, aspirin) in ovarian stimulation and whether these are recommended.

A lay version of the guideline is prepared and available on the ESHRE website www.eshre.eu/guidelines.

Introduction

Ovarian stimulation (OS) is defined as pharmacological treatment with the intention of inducing the development of ovarian follicles. It can be used for two purposes: (i) for timed intercourse or insemination and (ii) in assisted reproduction, to obtain multiple oocytes at follicular aspiration (Zegers-Hochschild *et al.*, 2017).

OS for IVF/ICSI has not been addressed by existing evidence-based guidelines. It is discussed briefly in the National Institute for Health and Care Excellence guideline on fertility problems and the Royal Australian, and New Zealand Colleges of Obstetricians and Gynaecologist have published a statement on OS in assisted reproduction. Based on the lack of guidelines, the ESHRE Special Interest Group Reproductive Endocrinology initiated the development of an ESHRE guideline focussing on all aspects of OS for IVF/ICSI.

The aim of this guideline is to provide clinicians with evidence-based information on the different options for OS for IVF/ICSI, taking into account issues such as the 'optimal' ovarian response, live birth rates (LBR), safety, patient compliance and individualization. In this guideline, special attention has also been given to pre- and adjuvant treatments in poor responders and the prevention of ovarian hyperstimulation syndrome (OHSS) in high responders.

Materials and Methods

The guideline was developed according to a well-documented methodology that is universal to ESHRE guidelines (Vermeulen *et al.*, 2017).

In short, 18 key questions were formulated by the Guideline Development Group (GDG) and structured in PICO format (Patient, Intervention, Comparison, Outcome). For each question, databases (PUBMED/MEDLINE and the Cochrane library) were searched from inception to 8 November 2018, with a limitation to studies written in English. From the literature searches, studies were selected based on the PICO questions, assessed for quality and summarized in evidence tables and summary of findings tables. The critical outcomes for this guideline are efficacy in terms of cumulative live birth rate (CLBR) per started cycle and LBR per started cycle, as well as safety in terms of moderate and/or severe OHSS. GDG meetings were organized where the evidence and draft recommendations were presented by the assigned GDG member and discussed until consensus was reached within the group.

Each recommendation was labelled as strong or conditional and a grade was assigned (Andrews *et al.*, 2013) based on the strength of the supporting evidence (High ⊕⊕⊕⊕—Moderate ⊕⊕⊕◯—Low ⊕⊕◯◯—Very low ⊕◯◯◯). In the absence of evidence, the GDG formulated no recommendation or a good practice point (GPP) based on clinical expertise (Table I).

The guideline draft and an invitation to participate in the stakeholder review were published on the ESHRE website. In addition, all relevant stakeholders received a personal invitation to review by e-mail. We received 168 comments from 39 reviewers, representing 21 countries, two national societies (British Fertility Society and working groups from ESHRE). All comments were processed by the GDG, either by adapting the content of the guideline and/or by replying to the reviewer. The review process was summarized in the review report, which is published on the ESHRE website (www.eshre.eu/guidelines).

This guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

Results

Key questions and recommendations

The current document summarizes all the key questions and the recommendations from the guideline 'ovarian stimulation for IVF/ICSI'. Further background information and the supporting evidence for each recommendation can be found in the full version of the guideline available at http://www.eshre.eu/Guidelines-and-Legal/Guidelines. For easy reference, a schematic overview of the guideline is prepared (Fig. 1).

Table I Interpretation of strong versus conditional recommendations in the GRADE approach.*

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.
	Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

*(Andrews *et al.*, 2013) GRADE: Grading of Recommendations Assessment, Development and Evaluation

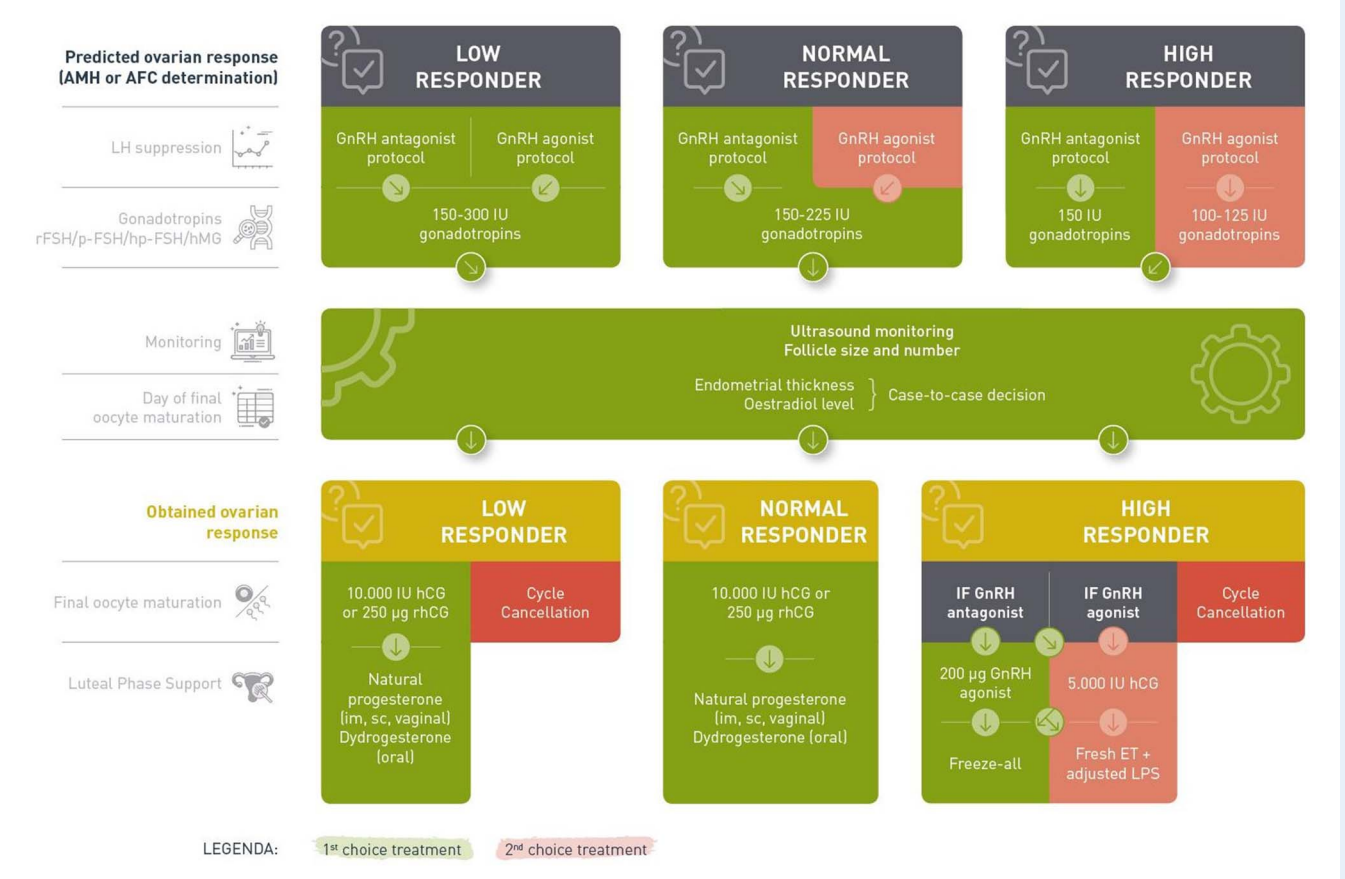

Figure 1 Schematic overview of the guideline 'ovarian stimulation for IVF/ICSI'. AMH: anti-Müllerian Hormone; AFC: antral follicle count; rFSH: recombinant FSH; p-FSH: purified FSH; hp-FSH: highly purified FSH; LPS: luteal phase support, ET: embryo transfer.

Ovarian response testing

For predicting high and poor response to OS, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests. (Broekmans *et al*., 2006, Broer *et al*., 2013a, Broer *et al*., 2013b)

Strong ⊕◯◯◯

The clinical implications of these tests regarding change in management with the purpose of improving efficacy and safety have not been evaluated by the GDG.

Assessment of progesterone level on Day 2 of the cycle at the start of OS is probably not recommended. (Panaino *et al*., 2017)

No recommendation can be given in view of the total lack of evidence on the prognostic role of baseline oestradiol in women undergoing OS for IVF/ICSI.

Conditional ⊕◯◯◯

Does hormone pre-treatment improve efficacy and safety of OS?

Pre-treatment with oestrogen before OS using the GnRH antagonist protocol is probably not recommended for improving efficacy and safety. (Farquhar *et al*., 2017)

Conditional ⊕◯◯◯

Pre-treatment with progesterone before OS is probably not recommended for improving efficacy and safety. (Farquhar *et al*., 2017)

Conditional ⊕⊕◯◯

The GDG acknowledges that oestrogen or progesterone is widely used for scheduling purposes. This is probably acceptable given the data on efficacy and safety.

GPP

Combined oral contraceptive pill (COCP) pre-treatment (12–28 days) is not recommended in the GnRH antagonist protocol because of reduced efficacy. (Farquhar *et al*., 2017)

Strong ⊕⊕◯◯

GnRH antagonist pre-treatment before OS in a delayed-start gonadotrophin protocol is probably not recommended. (Blockeel *et al*., 2011a; DiLuigi *et al*., 2011; Maged *et al*., 2015; Aflatoonian *et al*., 2017)

Conditional ⊕◯◯◯

LH suppression and OS

According to predicted response-based stratification, which stimulation protocol is most efficient and safe?

High responder

The GnRH antagonist protocol is recommended for women with polycystic ovary syndrome (PCOS), with regards to improved safety and equal efficacy. (Lambalk *et al*., 2017)	Strong ⊕⊕◯◯
The GnRH antagonist protocol is recommended for predicted high responders, with regards to improved safety and equal efficacy.	GPP
The addition of clomiphene citrate to gonadotrophins in stimulation protocols is probably not recommended for predicted high responders. (Lin *et al*., 2007; Saleh *et al*., 2014; Jiang and Kuang, 2017)	Conditional ⊕◯◯◯
There is insufficient evidence to recommend the addition of letrozole to gonadotrophins in stimulation protocols for predicted high responders. (Chen *et al*., 2018)	Conditional ⊕◯◯◯
The GnRH antagonist protocol is recommended for predicted high responders. However, if GnRH agonist protocols are used, a reduced gonadotrophin dose is probably recommended to decrease the risk of OHSS. (Oudshoorn *et al*., 2017)	Conditional ⊕◯◯◯
There is no evidence to justify the use of natural cycle or modified natural cycle for OS in predicted high responders.	

Normal responder

The GnRH antagonist protocol is recommended for predicted normal responder women, with regards to improved safety. (Lambalk *et al*., 2017)	Strong ⊕⊕◯◯
The addition of letrozole to gonadotrophins in stimulation protocols is probably not recommended for predicted normal responders. (Verpoest *et al*., 2006; Mukherjee *et al*., 2012)	Conditional ⊕◯◯◯
A reduced gonadotrophin dose is probably not recommended over a conventional gonadotrophin dose for predicted normal responders. (Hohmann *et al*., 2003; Baart *et al*., 2007, Blockeel *et al*., 2011b; Sterrenburg *et al*., 2011)	Conditional ⊕⊕◯◯
There is no evidence to recommend the use of clomiphene citrate in stimulation protocols for predicted normal responders.	

Poor responder

GnRH antagonists and GnRH agonists are equally recommended for predicted poor responders. (Xiao *et al*., 2013; Lambalk *et al*., 2017)	Conditional ⊕⊕◯◯
Clomiphene citrate alone or in combination with gonadotrophins and gonadotrophin stimulation alone is equally recommended for predicted poor responders. (Bechtejew *et al*., 2017)	Strong ⊕⊕◯◯
The addition of letrozole to gonadotrophins in stimulation protocols is probably not recommended for predicted poor responders. (Bechtejew *et al*., 2017)	Conditional ⊕⊕◯◯
It is unclear whether a higher gonadotrophin dose is recommended over 150 IU for predicted poor responders. (Lensen *et al*., 2017)	Conditional ⊕◯◯◯
A gonadotrophin dose higher than 300 IU is not recommended for predicted poor responders. (Lensen *et al*., 2017)	Strong ⊕◯◯◯
The use of modified natural cycle is probably not recommended over conventional OS for predicted poor responders. (Morgia *et al*., 2004)	Conditional ⊕◯◯◯
No studies were found comparing a reduced FSH dose (<150 IU/day) to conventional FSH stimulation in poor responders.	

Which LH suppression regimen is preferable?

If GnRH agonists are used, the long GnRH agonist protocol is probably recommended over the short or ultrashort GnRH agonist protocol. (Siristatidis *et al*., 2015)	Conditional ⊕⊕◯◯
The GnRH antagonist protocol is recommended over the GnRH agonist protocols given the comparable efficacy and higher safety in the general IVF/ICSI population. (Al-Inany *et al*., 2016)	Strong ⊕⊕⊕◯
The use of progestin for LH peak suppression is probably not recommended. If applied, progestin can only be used in the context of non-transfer cycles. (Kuang *et al*., 2015; Chen *et al*., 2017; Hamdi *et al*., 2018)	Conditional ⊕◯◯◯

Is the type of stimulation drug associated with efficacy and safety?

The use of recombinant FSH (rFSH) and hMG for OS is equally recommended. (van Wely *et al*., 2011)	Strong ⊕⊕⊕◯
The use of rFSH and purified FSH (p-FSH) for OS in GnRH agonist protocol is equally recommended. (van Wely *et al*., 2011)	Strong ⊕⊕◯◯
The use of either rFSH and highly purified FSH (hp-FSH) for OS in GnRH agonist protocol is equally recommended. (van Wely *et al*., 2011)	Strong ⊕⊕◯◯
The use of hp-FSH and hMG for OS in GnRH agonist protocols is equally recommended. (Duijkers *et al*., 1993; Westergaard *et al*., 1996; Parsanezhad *et al*., 2017)	Conditional ⊕⊕◯◯
The use of recombinant LH (rLH) + rFSH for OS is probably not recommended over hMG in GnRH agonist protocols with regards to safety. (Pacchiarotti *et al*., 2010)	Conditional ⊕◯◯◯

Letrozole is probably not recommended as a substitute for gonadotrophins in poor responders. (Verpoest *et al*., 2006; Yasa *et al*., 2013; Ebrahimi *et al*., 2017)	Conditional ⊕◯◯◯
The use of long-acting and daily rFSH is equally recommended in GnRH antagonist cycles for normal responders. (Griesinger *et al*., 2016a)	Strong ⊕⊕⊕◯
There is no evidence available to recommend the substitution of FSH by clomiphene citrate in OS.	

Is adjustment of the gonadotrophin dosage during the stimulation phase meaningful in terms of efficacy and safety?

Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during OS is probably not recommended. (van Hooff *et al*., 1993; Aboulghar *et al*., 2000; Cedrin-Durnerin *et al*., 2000; Aboulghar *et al*., 2004; Martin *et al*., 2006)	Conditional ⊕◯◯◯

Is the addition of adjuvants in OS meaningful in terms of efficacy and safety?

Routine use of adjuvant metformin before and/or during OS is not recommended with the GnRH antagonist protocol for women with PCOS. (Tso *et al*., 2014; Jacob *et al*., 2016)	Strong ⊕⊕◯◯
Use of adjuvant GH before and/or during OS is probably not recommended for poor responders. (Duffy *et al*., 2010; Li *et al*., 2017)	Conditional ⊕⊕◯◯
Use of testosterone before OS is probably not recommended for poor responders. (Nagels *et al*., 2015)	Conditional ⊕⊕⊕◯
Use of dehydroepiandrosterone before and/or during OS is probably not recommended for poor responders. (Nagels *et al*., 2015)	Conditional ⊕⊕⊕◯
Use of aspirin before and/or during OS is not recommended in the general IVF/ICSI population and for poor responders. (Siristatidis *et al*., 2016)	Strong ⊕⊕⊕◯
Use of sildenafil before and/or during OS is not recommended for poor responders. (Ataalla *et al*., 2017)	Strong ⊕◯◯◯
There is no evidence, i.e. controlled studies or randomised controlled studies (RCTs), addressing the efficacy and safety of adjuvant indomethacin use, to support a recommendation on the use of indomethacin during OS.	

What is the safety and efficacy of non-conventional start stimulation compared to standard early follicular phase stimulation?

Random-start OS is probably not recommended for the general IVF/ICSI population. (Pereira *et al*., 2017)	Conditional ⊕◯◯◯
Late luteal phase start of gonadotrophins is probably not recommended for poor responders. (Kuang *et al*., 2014; Zhang *et al*., 2016; Liu *et al*., 2017; Wu *et al*., 2017; Vaiarelli *et al*., 2018; Zhang *et al*., 2018)	Conditional ⊕◯◯◯
Early luteal phase start of gonadotrophins is probably not recommended for normal and poor responders. (Zhang *et al*., 2018)	Conditional ⊕◯◯◯
Luteal phase stimulation could be used in non-transfer cycles.	GPP
Double stimulation in poor responders should only be used in the context of clinical research.	Research only
Double stimulation can be considered for urgent fertility preservation cycles.	GPP

What is the preferred stimulation protocol for fertility preservation and freezing for social reasons?

For OS in women seeking fertility preservation for medical reasons, the GnRH antagonist protocol is probably recommended. (Boots *et al*., 2016; Rodgers *et al*., 2017)	Conditional ⊕◯◯◯
In urgent (oncology) fertility preservation cycles, random-start OS is an important option. (Boots *et al*., 2016)	Conditional ⊕◯⊕◯
In OS for fertility preservation in oestrogen-sensitive diseases, the concomitant use of anti-oestrogen therapy, such as letrozole or tamoxifen, can be considered.	GPP

Monitoring

Is the addition of hormonal assessment (oestradiol/progesterone/LH) to ultrasound monitoring improving efficacy and safety?

The addition of oestradiol measurements to ultrasound monitoring is probably not recommended. (Kwan *et al*., 2014)	Conditional ⊕⊕◯◯
The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring is probably not recommended. (Golan *et al*., 1994; Wiser *et al*., 2012)	Conditional ⊕◯◯◯

Does monitoring of endometrial thickness affect the efficacy and safety?

Routine monitoring of endometrial thickness during OS is probably not recommended. (Kasius *et al*., 2014)	Conditional ⊕◯◯◯
The guideline group suggests performing a single measurement of the endometrium during ultrasound assessment on the day of triggering or oocyte	GPP

retrieval to counsel patients on potential lower pregnancy chance.

Is the outcome of OS dependent on the criteria for triggering?

The association of follicle size as a triggering criterion with outcome has not been sufficiently studied.z Physicians may choose the follicle size upon which final oocyte maturation is triggered on a case to case basis. (Chen *et al*., 2014)	Conditional ⊕⊕◯◯
The decision on timing of triggering in relation to follicle size is multi-factorial, taking into account the size of the growing follicle cohort, the hormonal data on the day of pursued trigger, duration of stimulation, patient burden, financial costs, experience of previous cycles and organizational factors for the centre. Most often, final oocyte maturation is triggered at sizes of several of the leading follicles between 16 and 22 mm.	GPP
The GDG does not recommend to base timing of final oocyte maturation triggering on oestradiol levels alone.	GPP
The GDG does not recommended to base timing of final oocyte maturation on oestradiol/follicle ratio alone.	GPP

Which criteria for cycle cancellation are meaningful regarding predicted low/high oocyte yield?

A poor response to OS alone is not a reason to cancel a cycle. (Oudendijk *et al*., 2012)	Strong ⊕◯◯◯
The physician should counsel the individual poor responder regarding pregnancy prospects and decide individually whether to continue this and/or further cycles.	GPP
In GnRH agonist cycles with an ovarian response of ≥18 follicles, there is an increased risk of OHSS and preventative measures are recommended, which could include cycle cancellation. (Griesinger *et al*., 2016b, Mathur *et al*., 2000; Papanikolaou *et al*., 2006; Steward *et al*., 2014)	Strong ⊕◯◯◯

Triggering ovulation and luteal support

What is the preferred drug for triggering of final oocyte maturation in terms of efficacy and safety in the overall IVF/ICSI population?

The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation during OS protocols. (Youssef *et al*., 2016)	Strong ⊕⊕◯◯
A reduced-dose of 5000 IU urinary hCG for final oocyte maturation is probably recommended over a 10 000 IU dose in GnRH agonist protocols, as it may improve safety. (Shaltout *et al*., 2006; Kolibianakis *et al*., 2007; Madani *et al*., 2013)	Conditional ⊕◯◯◯
It is not recommended to administer rLH for triggering final oocyte maturation. (Youssef *et al*., 2016)	Strong ⊕◯◯◯
The use of GnRH agonist for final oocyte maturation with conventional luteal support and fresh transfer is not recommended in the general IVF/ICSI population. (Griesinger *et al*., 2006)	Strong ⊕⊕◯◯
The use of GnRH agonist for final oocyte maturation, luteal support with LH-activity and fresh transfer is probably not recommended for the predicted normal responder. (Humaidan *et al*., 2006; Humaidan *et al*., 2010; Papanikolaou *et al*., 2011; Humaidan *et al*., 2013)	Conditional ⊕◯◯◯
If the GnRH agonist trigger with triptorelin is applied, dosages ranging from 0.1 to 0.4 mg can be chosen. (Vuong *et al*., 2016)	GPP
The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for predicted normal responders. (Ding *et al*., 2017)	Conditional ⊕⊕◯◯
There are no studies investigating the direct comparison of hCG with different dosages of GnRH agonist trigger with buserelin or leuprolide. No controlled studies or RCT could be found comparing different dosages of buserelin or leuprolide for final oocyte maturation. Therefore, no recommendation can be formulated regarding optimal dosage.	

What is the efficacy and safety of luteal support protocols?

Progesterone is recommended for luteal phase support after IVF/ICSI. (van der Linden *et al*., 2015)	Conditional ⊕◯◯◯
Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used.	GPP
The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 mg once daily for i.m. progesterone 25 mg once daily for s.c. progesterone 90 mg once daily for vaginal progesterone gel 200 mg three times daily for micronized vaginal progesterone in-oil capsules 100 mg two or three times daily for micronized vaginal progesterone in starch suppositories 400 mg two times daily for vaginal pessary.	GPP
Starting of progesterone for luteal phase support should be in the window between the evening of the day of oocyte retrieval and Day 3 post oocyte retrieval.	GPP
Progesterone for luteal phase support should be administered at least until the day of the pregnancy test.	GPP

Dydrogesterone is probably recommended for luteal phase support. (Barbosa *et al*., 2018)	Conditional ⊕⊕⊕◯
The addition of oestradiol to progesterone for luteal phase support is probably not recommended. (van der Linden *et al*., 2015)	Conditional ⊕⊕◯◯
In hCG triggered OS cycles, hCG as luteal phase support in standard dosages of 1500 IU is probably not recommended. (van der Linden *et al*., 2015)	Conditional ⊕⊕◯◯
A GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles, can only be used in the context of a clinical trial.	Research only
Repeated GnRH agonist injections, alone or in addition to progesterone for luteal phase support in hCG triggered cycles, can only be used in the context of a clinical trial.	Research only
Addition of LH to progesterone for luteal phase support can only be used in the context of a clinical trial.	Research only

Prevention of OHSS

Which GnRH agonist medication as a method of triggering will add to the prevention of OHSS also with regards to overall efficacy

A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS (Babayof *et al*., 2006; Engmann *et al*., 2008; Humaidan *et al*., 2013; Youssef *et al*., 2014)	Strong ⊕◯◯◯
A freeze-all strategy is recommended to eliminate the risk of late-onset OHSS and is applicable in both GnRH agonist and GnRH antagonist protocols.	GPP
If a GnRH agonist trigger with freeze-all strategy is not used in patients at risk of OHSS, it is not clear whether the use of a 5000 IU hCG trigger or GnRH agonist trigger is preferred. The GnRH agonist trigger should be followed by luteal phase support with LH-activity (Humaidan *et al*., 2013)	Conditional ⊕◯◯◯
In patients at risk of OHSS, the use of a GnRH agonist for final oocyte maturation is probably recommended over hCG in cases where no fresh transfer is performed (Borges *et al*., 2016; Tannus *et al*., 2017)	Conditional ⊕◯◯◯
A GnRH agonist trigger for final oocyte maturation with or without a freeze-all strategy is preferred over a coasting strategy in patients at risk of OHSS.	GPP
Cabergoline or albumin as additional preventive measures for OHSS is not recommended when GnRH agonist is used for triggering final oocyte maturation.	GPP

Is the freeze-all protocol meaningful in the prevention of OHSS also with regard to efficacy?

A freeze-all strategy is recommended to fully eliminate the risk of late-onset OHSS (Wong *et al*., 2017)	Strong ⊕⊕⊕◯
Prior to start of OS, a risk assessment for high response is advised.	GPP

Discussion

This ESHRE guideline on OS for IVF/ICSI aims to supply healthcare providers with the best available evidence for approaches in the various steps and phases of OS for IVF/ICSI.

All recommendations in the guideline were formulated after an assessment of the best available evidence in the literature and discussion within the GDG, taking into account the balance of benefits versus harms, patient preferences, clinicians' expertise and resource use. The guideline includes 84 recommendations, including 61 evidence-based recommendations—of which 21 were formulated as strong recommendations and 40 as conditional—and 19 GPPs and four research only recommendations. The evidence supporting OS was often limited and of low quality. Of the evidence-based recommendations, only eight (13.1%) were supported by moderate quality evidence. The remaining recommendations were supported by low- (22 recommendations: 36.1%) or very low-quality evidence (31 recommendations: 50.8%). There were no recommendations based on high-quality evidence.

One of the difficulties the guideline group encountered when collecting and interpreting the available evidence was the lack of uniform definitions of a high and poor response. Despite the definitions of poor response provided by the Bologna consensus paper (Ferraretti *et al*., 2011) and the ICMART glossary (Zegers-Hochschild *et al*., 2017), numerous publications still use a slightly different definition, complicating the interpretation and comparison of data between publications. Similarly, despite several key publications demonstrating the connection between a high number of retrieved oocytes and the risk of OHSS, definitions of high response differ greatly between publications and are often ill-defined within the publications.

One of the most important consequences of the limited evidence is the absence of evidence for interventions aimed at improving OS in poor responders. For most of these interventions, such as adjuvant therapies, there are limited and often very low-quality data. Despite this lack of evidence, several of these adjuvant therapies are regularly administered to women experiencing poor ovarian response. Similarly, there is very limited evidence regarding gonadotrophin dosages in poor responders, yet, high dosages are commonly used without evidence-based motivation. Until large RCTs have been conducted on these interventions, the GDG formulated recommendations against these interventions or dosing levels.

Another consequence of the limited evidence is the number of recommendations specifying (newer) interventions to be applied in a research context rather than routine clinical practice. The current guideline contains four recommendations on interventions to be applied in a research context only. A controversial example of a research-only recommendation is the use of double stimulation, specifically for poor responders.

The current guideline clearly exposes areas where more research is necessary and a research agenda has been developed, with the aim of stimulating research on OS and more specifically on the questions in urgent need of an answer (Fig. 2). While awaiting evidence and

From the literature and discussion of the available evidence, several topics were identified for which evidence is inconsistent, insufficient or non-existing. For the benefit of couples undergoing ovarian stimulation for IVF/ICSI, the GDG recommends that future research, where possible in well-designed RCTs, should focus on these research gaps.

Considered are:

- Gonadotrophin dose reduction in predicted high responders as a tool for normalization of ovarian response (GnRH agonist or antagonist) compared to a standard dosage with option GnRH agonist trigger and/or a freeze-all strategy (in GnRH antagonist protocol).
- Pre-treatment options for scheduling in GnRH antagonist protocol compared to GnRH agonist protocol
- Luteal phase support: GnRH agonist compared to progesterone compared to low dose hCG
- The efficacy and safety of a freeze-all strategy in cycles with routine embryo biopsy for PGT
- GnRH agonist trigger with adjusted luteal support compared to 10.000 hCG trigger with freeze-all in observed high responder

Figure 2 Recommendations for research in ovarian stimulation for IVF/ICSI.

evidence-based recommendations, GPPs are provided to support clinicians in routine practice.

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Authors' roles

F.B. chaired the guideline development group and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. N.L.C., as methodological expert, performed all literature searches for the guideline, provided methodological support and coordinated the guideline development. All other authors, listed in alphabetical order, as guideline group members, contributed equally to the manuscript, by drafting key questions, synthesizing evidence, writing the different parts of the guideline and discussing recommendations until consensus within the group was reached. All authors approved of the final version of the guideline.

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Conflict of interest

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