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Ovarian stimulation for IVF/ICSI

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Guideline of European Society of Human Reproduction and Embryology

The ESHRE Ovarian Stimulation Guideline Group

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The European Society of Human Reproduction and Embryology (hereinafter referred to as 'ESHRE') developed the current clinical practice guideline, to provide clinical recommendations to improve the quality of healthcare delivery within the European field of human reproduction and embryology. This guideline represents the views of ESHRE, which were achieved after careful consideration of the scientific evidence available at the time of preparation. In the absence of scientific evidence on certain aspects, a consensus between the relevant ESHRE stakeholders has been obtained.

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Annex 7: Literature study: flowcharts, list of excluded studies **Separate document**

Annex 8: Evidence tables **Separate document**

Introduction to the guideline

Ovarian stimulation for *in vitro* fertilisation/Intracytoplasmic sperm injection (IVF/ICSI) has not been addressed by existing evidence-based guidelines. Ovarian stimulation for IVF/ICSI has been discussed briefly in the NICE guideline on Fertility problems (https://www.nice.org.uk/guidance/cg156) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologist has published a statement on ovarian stimulation in assisted reproduction (https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20Gynaecology/Ovarian-Stimulation-in-infertility-(C-Gyn-2)-Review-Mar-14.pdf?ext=.pdf).

A narrative review of evidence provided for WHO guidance on management of ovarian stimulation for IVF was published in 2017, but this document did not include recommendations (Farquhar et al., 2017).

Based on the lack of guidelines, the ESHRE SIG Reproductive Endocrinology initiated the development of an ESHRE guideline focussing on all aspects of ovarian stimulation, which was published in 2019 (Ovarian Stimulation et al., 2020).

The current guideline is an update of the version from 2019, with amendments to the recommendations based on recently published data. Where amendments were made, based on new evidence, this is labelled as such [updated]. If the GDG felt rewording of a recommendation was necessary without new evidence on the topic, this was indicated with [reworded].

The 2019 guideline and the update are developed according to a well-documented methodology, universal to ESHRE guidelines and described in the Manual for ESHRE guideline development (www.eshre.eu). Details on the methodology of the current guideline are outlined in Annex 4.

The guideline development group (GDG) for the current update consisted of the previous guideline group with minor changes. Two members of the GDG (2019) decided to step down and were replaced by one new member. The members of the guideline development group are listed in Annex 1.

GUIDELINE SCOPE

The aim of this guideline is to provide clinicians with evidence-based information on the different options for the performance of ovarian stimulation for IVF/ICSI, taking into account issues such as the 'optimal' ovarian response, live birth rates, safety, patient compliance, and individualisation. Knowledge gaps were identified and prioritized.

The following issues were outside the scope of the current document: patients with specific medical conditions (except for PCOS), and treatment of the ovarian hyper-stimulation syndrome (OHSS).

TARGET USERS OF THE GUIDELINE

Infertility specialists and specialty nurses performing the daily care for patients undergoing ovarian stimulation for the purpose of IVF/ICSI.

TERMINOLOGY

Ovarian stimulation is defined as pharmacological treatment with the intention of inducing the development of ovarian follicles and trigger the ovulation process of these follicles. It can be used for two purposes: 1) for timed intercourse or insemination; 2) for IVF/ICSI, to obtain multiple oocytes at follicular aspiration (Zegers-Hochschild et al., 2017). The GDG decided to use the term ovarian stimulation (OS) confined to ovarian stimulation for IVF/ICSI.

The GDG would also like to point to the importance of 'simplicity of ovarian stimulation'. When comparing compounds, dosages or add-on treatments for ovarian stimulation in this guideline document, preference was always given to the more basic option, unless a clear benefit of more complex treatments was shown.

Response after ovarian stimulation is usually classified as poor, normal and excessive. However, this terminology can be potentially stigmatising/traumatising towards patients. Therefore, the GDG would like to propose to use the terminology low, normal and high response to categorize (the observed as well as the expected/predicted) response to OS for future referencing. However, the definition of low response proposed in this guideline is the same as the definition of the Bologna poor responder and the poor responder as defined by ICMART (Ferraretti et al., 2011, Zegers-Hochschild, et al., 2017).

Due to the lack of universally accepted definitions of high and low ovarian response, the definitions and terminology in the studies included in the evidence synthesis were varied. However, for future practice and research, the GDG suggests using the following definitions:

- High ovarian response is an exaggerated response to conventional ovarian stimulation (150-225 IU FSH), characterized by the presence of more follicles and/or oocytes than intended (Griesinger et al., 2016). Generally, more than 18 follicles ≥11 mm in size on day of oocyte maturation trigger and/or 18 oocytes collected characterize a high response (Griesinger, et al., 2016), defined by a risk increase for OHSS occurrence.
- Low ovarian response is a diminished response to conventional ovarian stimulation, characterized by the presence of a low number of follicles and/or oocytes (Ferraretti, et al., 2011). Generally, ≤ 3 follicles on day of oocyte maturation trigger and/or ≤ 3 oocytes obtained characterize a low response.

In this guideline, in line with the research, terminology and discussion on ovarian stimulation is focused on women. The guideline group recognises that there are individuals who do not identify with the terms used in the literature. For the purposes of this guideline, we use the terms "women", "patients", "low/poor responder", "normal responder" and "high responder", however, it is not intended to isolate, exclude, or diminish any individual's experience nor to discriminate against any group.

Outcomes for this guideline

The guideline focuses on outcomes of efficacy, safety and patient-related outcomes.

The critical outcomes for this guideline are **efficacy** in terms of cumulative live birth rate (CLBR) per started cycle and live birth rate (LBR) per started cycle; and **safety** in terms of the risk of moderate and/or severe OHSS.

Other outcomes used for efficacy were (in order of importance) cumulative ongoing pregnancy rate per started cycle, clinical pregnancy rate per started cycle, number of MII oocyte retrieved (yield), number of oocytes retrieved.

Other outcomes used for safety include incidence of different grades of OHSS, cycle cancellation for hyper-response, intra-abdominal or vaginal bleeding, infection, ovarian torsion, long-term effects on maternal/child health, and other treatment-related adverse events.

Patient-related outcomes are compliance, drop-out rates, patient burden, quality of life (QoL), and patient preferences.

All outcomes were defined, where possible, as per started cycle.

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Introduction

IVF: the purpose and significance.

Infertility is a disease state with potential profound consequences for the quality of life of both men and women. Reproduction is one of the key elements of life and failing to achieve the creation of offspring may lead to lifelong mental and physical health problems. Also, couples faced with infertility are frequently subjected to long-lasting, time consuming and agonizing treatment schedules, living often between hope, fear and frustration (Brandes et al., 2010, Brandes et al., 2009, Gameiro and Finnigan, 2017). The development of IVF as a tool for treating infertility as a result of tubal disease, severe male factor causes, anovulation and even, although not convincingly proven, conditions like unexplained infertility, has brought enormous potential to the infertility treatment armamentarium. Still, of all couples visiting infertility centres, roughly 35-40% will not achieve the so desired goal, in spite of lengthy efforts, including IVF, and most of these couples will remain permanently childless (McLernon et al., 2016, Olivius et al., 2002). This indicates that currently we still have areas of low-level knowledge on the key factors of success, such as gamete quality, embryo quality and endometrial receptivity. Improving the IVF technology may well depend on progress in these fields of research.

Stimulation: how important is it.

Very soon after the development of the IVF technology, performing IVF in a natural menstrual cycle was superseded by the use of ovarian stimulation in order to obtain multiple oocytes. This was aimed at solving two problems: one was the elimination of the risk of having no oocyte at all. The other was the urge to improve efficiency by obtaining several embryos and replacing the best quality embryo(s) to improve the probability of pregnancy. Ovarian stimulation has thereby become one of the cornerstones of the IVF treatment, next to the *in vitro* handling of gametes and embryos, and the embryo replacement procedure. The relative contribution to the overall success of IVF by the ovarian stimulation phase is difficult to assess. Many years of research have aimed at optimizing this specific phase. Many issues have been addressed, ranging from using urinary FSH products or recombinants, using high or low FSH dosages, final oocyte maturation with urinary of recombinant, high or low dosage of hCG, adding LH or LH-like activity to the FSH as principal drug, management of high and low responders, to the use of adjuvant medications to improve follicle availability and quality, etcetera. At the same time, debates have been there on strong beliefs, like “the more (oocytes) the better”, less (mild stimulation) is more (quality), “normal (8-17 oocytes) is the best”, and “we need eggs, not ALL the eggs”. It seems that agreement on the optimal ovarian stimulation approach, aimed at getting more than 1 oocyte, as in the normal menstrual cycle, is far from settled.

Basics: FSH elevation.

Complex as it seems, the endocrine background for ovarian stimulation is quite straightforward. FSH levels must become elevated above the level that normally will help to select and grow ONE follicle out of a group of antral follicles presenting in the FSH ‘window’. During this window, levels of FSH surpass a certain threshold above which follicle granulosa cells become responsive for proliferative actions, leading to expansion of the granulosa cell mass and the follicle fluid volume, typically of only one follicle, while other potential responsive follicles continue to enter and proceed the stages of atresia. In surpassing the threshold to a greater extent, and for a much longer period of time with the use of

ovarian stimulation, more than one follicle will become capable of entering this dominant follicle development stage. The tools available for increasing FSH exposure are several, but basically most comprise preparations containing FSH. The source of FSH can be urinary (purified or highly purified) or recombinant (the FSH molecule is produced by programmed cells from hamster, mouse or human). Some preparations combine FSH with LH, or LH-like activity (hCG). The vast majority of FSH compounds are distributed for dosing in International Units, a standardisation based on an oestradiol output bio-assay. Two compounds are delivered in micrograms, and their dosing is based on age and bodyweight..

Apart from administering FSH as an exogenous drug, compounds such as selective oestradiol receptor blockers or oestradiol biosynthesis inhibitors may yield the same effect: increased and prolonged FSH exposure.

Source: Ovarian Antral Follicles, continuous versus cyclic recruitment.

The follicles presenting in the window of elevated FSH levels are part of a continuous recruitment process. Starting from the resting pool of primordial follicles, follicles develop through several phases, reaching the antral stages after approximately 200 days (McGee and Hsueh, 2000). At that time point they attain relevant FSH sensitivity. Without FSH exposure, such as in the prepubertal years, these follicles will reach maximum sizes of 2-3 mm and vanish into the process of atresia. Without any FSH exposure, this wastage process would continue until around the age of 50 years, when the ovarian primordial follicle pools will have become depleted. It is the presence of FSH in varying levels that allows the ovaries to pick up follicles in the antral stages, which become more prominent at ultrasound, and from there deliver the ovulating follicle of the month, or, as in ovarian stimulation, recruit several to many follicles from those that present in the window of opportunity to respond to FSH. This ovarian activity is referred to as cyclic recruitment. The number of follicles that present in the opportunity window of cyclic recruitment is highly variable between women and between age groups. As a general rule, the number of antral follicles that can be stimulated will decline gradually with increasing age, as an expression of the shrinking pool of primordial follicles.

Store of Antral Follicles: can we manipulate it?

Obtaining only few oocytes is often considered an agonizing condition, as it may affect the prospects for a live birth in IVF, albeit that this prospect is also very much determined by the age of the woman. Still, there is a continuous search for methods to improve the egg number in low responders, and from the aforementioned, it can be deduced that such method should interfere with early stages of follicle development, where initial recruitment and/or later survival during continuous recruitment is promoted. Numerous strategies and interventions have been suggested to enhance this sequence of events; however, clinically useful strategies are still awaited, although more oocytes in this group may not likely affect their quality.

Oocyte number and Dosage: what is the relation like?

The cohort of antral follicles being the finite source for oocytes, the level of exposure to FSH may add to the total number of oocytes obtained. With the need of a minimum exposure to grow more than 1 follicle, there seems to be a positive relation between FSH dosage and oocyte yield, ranging from about 50 IU daily for a minimal response of 2 oocytes up to about 225 IU to obtain a maximal response (Lensen et al., 2017, Sterrenburg et al., 2011). **Although systematic reviews of randomized controlled trials (RCTs) found higher oocyte yield with higher stimulation dose, all RCTs that compared the mean number or proportion of high-grade embryos between low (≤ 150 IU) and higher dose found no difference in poor as well as normal responder patients** (Datta et al., 2021). For the optimal response

level in terms of oocytes a daily dosage of 150 to 225 IU is mostly considered as standard. This implies that when using a stimulation dosage of 150 IU per day and creating a low follicle response, the range of opportunities in dose adjustments is likely to be limited. This is certainly much dependant on the of Antral Follicle Count or AMH result. With test results below a certain level, the so called predicted low responder may not produce more oocytes with a higher FSH dosage. With AFC and/or AMH levels within the normal range, an unexpected low responder may well obtain more oocytes with a higher FSH dosage. The question then remains whether more oocytes will improve the prospects for a live birth? We still need to see evidence that a few oocytes more or less will make the desired or feared difference in terms of live birth rates. At this point it may be emphasized that the various cross-sectional cohort data on the relation between oocyte number and cumulative live birth rates have suggested that 'more is better' and 'less is bad'. These observations are correlation data, without the possibility to conclude that there is a causal relationship. With respect to the latter, we may reflect on the implications of many randomised comparative trials demonstrating that a few more or less oocytes within the individual couple will fail to make an obvious difference in the live birth prospects.

At the other side of the spectrum, a high response to a standard dosage of 150 IU may be undesirable as it is a potential source for the development of the Ovarian Hyperstimulation Syndrome (OHSS), even today a potentially life-threatening condition. Reduction of the FSH stimulation dosage may bring a more mitigated response, with better safety, without jeopardizing overall live birth prospects. However, it is to be understood that the driver of the syndrome occurring in high responder cases in fact is the exposure of the granulosa cells to human chorionic gonadotropin (hCG). Necessary as this may be for the final oocyte competence attainment, circumventing administration of this drug by creation of an endogenous LH surge by applying a GnRH agonist trigger is certainly a powerful way to decrease the risk of OHSS. Finally, prevention of pregnancy-derived hCG to occur by freezing all embryos is another important and logical step.

Control on ovulation: agonists and antagonist.

When stimulating the ovaries to create multifollicular development, the fast-rising oestradiol levels may elicit an untimely LH surge. Untimely, as follicles may not have grown sufficiently large to ensure the best quality oocytes, and when passed unnoticed, oocyte pick up may become a failed procedure. The use of agents that block the signalling by the GnRH pulse generator towards the pituitary, such as GnRH agonists, GnRH antagonists and progestins, have almost completely ruled such mishaps and have greatly contributed to the efficiency of ovarian stimulation for IVF/ICSI.

Oocytes, and then?

Although the primary goal of ovarian stimulation is obtaining several oocytes, the timed replacement of the embryo necessitates parallel and physiologically correct development of the endometrium. Implantation is dependent on proper endocrine conditions, such as oestradiol exposure, in order to ensure proliferation, and progesterone exposure commencing around ovulation in order to have the endometrium differentiated into a receptive state. Stimulation per se is a guarantee for oestradiol synthesis and release from the many developing follicles. The LH peak, or as in many cases, hCG exposure, will enable granulosa cell differentiation into a progesterone producing system, that, in normal condition, will be driven by continued endogenous LH pulses. In the GnRH agonist suppression and GnRH antagonist approach, the interference with the GnRH receptor will lead to LH levels dropping to low levels, and the hCG exposure here takes over the role of LH in maintaining luteal function up till maximally 7-9 days after the ovulation trigger. On top of that, supraphysiological exposure to

endogenous oestradiol and progesterone, driven by the exogenous administration of FSH and later hCG, will further add in the insufficiency of the pituitary to produce the amounts of LH needed for continued support of the corpora lutea. As such, luteal support is almost exclusively applied in the form of exogenous natural progesterone, which is initiated often already at the day of follicle aspiration. However, pharmacokinetics may not always be very stable for these compounds, and when endogenous LH exposure by using an GnRH agonist trigger is applied, instead of the hCG signal, luteal phase becomes insufficient in many cases even with the current exogenous progesterone administration. The luteal phase support approach therefore remains an important area of research for improvement of the quality of the embryo implantation phase.

Many years of basic and clinical research have delivered us tools for ovarian stimulation that make this procedure effective, efficient, safe and an essential contribution to the total process of Assisted Reproduction. In this guideline, important knowledge is brought together using a set of relevant questions, for which searches and selections of the literature, grading of the knowledge base regards quality, and well-balanced recommendations will provide the best possible answers to the question. These recommendations will help clinicians to decide on what best to do or better not to do in clinical conditions where we wish to provide optimal care to our patients.

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List of all recommendations

	Recommendation	Strength	Quality of evidence	Remarks
Part A: Pre-stimulation evaluation				
Ovarian response prediction				
1	For predicting high and low response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended. [updated]	Strong	⊕◯◯◯	
2	Age, BMI, basal FSH, inhibin B, basal oestradiol, basal progesterone and basal LH are not recommended for the prediction of ovarian response. [2025]	Strong	⊕◯◯◯	
Pregnancy prediction				
3	AFC, AMH, basal FSH, basal LH, basal oestradiol, basal progesterone and inhibin B are not recommended for the prediction of pregnancy and live birth. [updated]	Strong	⊕◯◯◯	
4	Female age and BMI are predictors of pregnancy and live birth. [2025]	Strong	⊕◯◯◯	
Part B: Pre-treatment therapies				
Pre-treatment therapies				
5	Pre-treatment with oestrogen before ovarian stimulation using the GnRH antagonist protocol is not recommended for improving efficacy. [updated]	Strong	⊕⊕◯◯	SoF table 1 a,b
6	Pre-treatment with progesterone before ovarian stimulation is probably not recommended for improving efficacy. [reworded]	Conditional	⊕⊕◯◯	SoF table 2 a,b
7	Oestrogen or progesterone pre-treatment can be used for scheduling purposes given the data on efficacy and safety. [reworded]	GPP		
8	COCP pre-treatment is not recommended in the GnRH antagonist protocol with FSH alone stimulation, because of reduced efficacy. [updated]	Strong	⊕⊕◯◯	SoF table 3 a,b,c
9	A minimal wash out period of 5 days may be applied if COCP is used for programming cycle in the case of a fresh transfer. [2025]	GPP		
10	GnRH antagonist pre-treatment before ovarian stimulation in a delayed-start gonadotrophin protocol is probably not recommended. [2019]	Conditional	⊕◯◯◯	SoF table 4 a,b
11	hCG pre-treatment can only be used in the context of a clinical trial. [2025]	Research only		

Part C: Pituitary suppression and ovarian stimulation

Stimulation protocols

12	Delayed-start ovarian stimulation is probably not recommended routinely in predicted high responders to decrease the risk of OHSS. [2025]	Conditional	⊕◯◯◯	SoF table 5
/	There is no evidence to justify the use of NC or MNC for OS in high responders.	/	/	Conclusion
13	A reduced gonadotropin dose (100 to <150 IU) is probably recommended to decrease the risk of OHSS in predicted high responders. [2025]	Conditional	⊕◯◯◯	SoF table 6
14	The GnRH antagonist protocol is recommended for predicted high responders. [updated]	Strong	⊕◯◯◯	
15	Delayed-start ovarian stimulation is probably not recommended over a conventional gonadotrophin dose for predicted normal responders. [2025]	Conditional	⊕◯◯◯	SoF table 7
16	Neither a reduced nor increased gonadotrophin dose is probably recommended over a conventional gonadotrophin dose (equivalent to 150-225 IU) for predicted normal responders. [updated]	Conditional	⊕◯◯◯	SoF table 8
17	Delayed start ovarian stimulation is probably not recommended for predicted low responders. [2025]	Conditional	⊕◯◯◯	SoF table 9
18	The use of modified natural cycle is probably not routinely recommended over conventional stimulation for low responders. [updated]	Conditional	⊕◯◯◯	
19	The GDG recognises that low responders are a heterogeneous group and in women with very low ovarian reserve, clinicians could choose to use a modified natural cycle. [2025]	GPP		
20	A gonadotropin dose higher than 300 IU is not recommended for predicted low responders. [2019]	Strong	⊕◯◯◯	

Pituitary suppression regimens

21	If GnRH agonists are used, the long GnRH agonist protocol is recommended over the short or ultrashort GnRH agonist protocol. [updated]	Strong	⊕⊕◯◯	SoF table 11 a,b
22	The GnRH antagonist protocol is recommended over the GnRH agonist protocols given the comparable efficacy and higher safety in the general IVF/ICSI population. [2019]	Strong	⊕⊕⊕◯	SoF table 12 a,b
23	The fixed GnRH antagonist protocol is probably recommended over the flexible GnRH antagonist protocol. [2025]	Conditional	⊕⊕◯◯	
24	If freeze-all is planned, the use of progestin for pituitary suppression is probably equally recommended to GnRH analogues. [updated]	Conditional	⊕◯◯◯	SoF table 13 a,b,c,d

Types of gonadotropins and other ovarian stimulation drugs

25	The use of recombinant human FSH (r-hFSH) and human menopausal gonadotropin (hMG) for ovarian stimulation is equally recommended. [2019]	Strong	⊕⊕⊕◯	SoF table 14

26	The use of recombinant human FSH (r-hFSH) and purified FSH (p-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended. [2019]	Strong	⊕⊕◯◯	SoF table 15
27	The use of either recombinant human FSH (r-hFSH) and highly purified FSH (hp-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended. [2019]	Strong	⊕⊕◯◯	SoF table 16
28	The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for the general IVF population. [2025]	Conditional	⊕⊕◯◯	SoF table 17a
29	The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for low responders. [2025]	Conditional	⊕⊕◯◯	SoF table 17b
30	The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for women of advanced age (≥35 year). [2025]	Conditional	⊕⊕◯◯	SoF table 17c
31	The combined use of recombinant human FSH (r-hFSH) with human menopausal gonadotropin (hMG), either from the start or mid-phase of ovarian stimulation, is probably not recommended over the use of either r-hFSH or hMG alone in normal and low responders. [2025]	Conditional	⊕⊕◯◯	SoF table 18 a,b
32	The use of long-acting and daily recombinant human FSH (r-hFSH) is equally recommended in GnRH antagonist cycles for normal responders. [2019]	Strong	⊕◯◯◯	SoF table 19
33	Follitropin delta and follitropin alpha/beta are equally recommended for ovarian stimulation. [2025]	Strong	⊕◯◯◯	
34	The use of highly purified FSH (hp-FSH) and human menopausal gonadotropin (hMG) for ovarian stimulation in GnRH agonist protocols is equally recommended. [2019]	Conditional	⊕⊕◯◯	
35	The use of recombinant human LH + recombinant human FSH (r-hFSH+r-hLH) for ovarian stimulation is probably not recommended over human menopausal gonadotropin (hMG) in GnRH agonist protocols with regards to safety. [2019]	Conditional	⊕◯◯◯	
36	Adding low dosages of hCG to the FSH stimulation is probably not recommended. [2025]	Conditional	⊕◯◯◯	SoF table 20 a,b,c
37	The addition of letrozole to gonadotropins in stimulation protocols for predicted high responders is probably not recommended. [updated]	Conditional	⊕◯◯◯	SoF table 21 a
38	The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders. [2019]	Conditional	⊕◯◯◯	SoF table 21 b
39	The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted low responders. [2019]	Conditional	⊕⊕◯◯	
/	There is no evidence available to recommend the substitution of FSH by Clomiphene Citrate in ovarian stimulation.	/	/	Conclusion
40	The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted high responders. [2019]	Conditional	⊕⊕◯◯	SoF table 22 a
41	The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders. [2025]	Conditional	⊕⊕⊕◯	SoF table 22 b

42	Clomiphene citrate alone or in combination with gonadotrophins, and gonadotropin stimulation alone are probably equally recommended for predicted low responders. [updated]	Conditional	⊕⊕◯◯	

Adjustment of gonadotropin dose

43	Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during ovarian stimulation is probably not recommended. [2019]	Conditional	⊕◯◯◯	
44	Given the lack of evidence of the value of dose adjustments during ovarian stimulation, it is important that the gonadotropin starting dose is appropriate based on patient characteristics and desired outcome. [2025]	GPP		

Adjunct therapies

45	Routine use of adjunct metformin before and/or during ovarian stimulation is probably not recommended when using the GnRH antagonist protocol for women with PCOS. [Updated]	Conditional	⊕⊕◯◯	SoF table 23
46	Use of adjunct growth hormone before and/or during ovarian stimulation is not recommended for normal responders. [2025]	Strong	⊕◯◯◯	SoF table 24 a
47	Use of adjunct growth hormone before and/or during ovarian stimulation is probably not recommended for low responders. [Updated]	Conditional	⊕◯◯◯	SoF table 24 b
48	Use of adjunct growth hormone before and/or during ovarian stimulation is not recommended for women with PCOS. [2025]	Strong	⊕⊕◯◯	
49	Use of testosterone before ovarian stimulation is probably not recommended for low responders. [updated]	Conditional	⊕⊕⊕◯	SoF table 25
50	Use of DHEA before and/or during ovarian stimulation is not recommended for low responders. [2019]	Strong	⊕⊕◯◯	SoF table 26
51	Use of DHEA before and/or during ovarian stimulation is not recommended for normal responders. [2025]	Strong	⊕⊕◯◯	
52	Use of aspirin before and/or during ovarian stimulation is not recommended in the general IVF/ICSI population nor for low responders. [2019]	Strong	⊕⊕⊕◯	SoF table 27
53	Use of sildenafil before and/or during ovarian stimulation is not recommended for low responders. [2019]	Strong	⊕◯◯◯	
54	Use of myo-inositol before and/or during ovarian stimulation is probably not recommended for women with PCOS undergoing IVF. [2025]	Conditional	⊕◯◯◯	SoF table 28 a
55	Use of myo-inositol before and/or during ovarian stimulation is not recommended in low responders. [2025]	Strong	⊕⊕◯◯	
56	Use of myo-inositol before and/or during ovarian stimulation is not recommended in non-PCOS women undergoing IVF. [2025]	Strong	⊕⊕◯◯	SoF table 28 b

Non-conventional start of ovarian stimulation

57	Random-start ovarian stimulation could be used when a fresh transfer is not intended; nonetheless, the risk of OHSS in case of concurrent spontaneous conception should always be discussed with the patient. [Reworded]	GPP		

58	Luteal start ovarian stimulation could be used when a fresh transfer is not intended and there is no possibility of natural conception. [Updated]	Conditional	⊕◯◯◯
59	Late luteal phase start of gonadotropins with fresh transfer is probably not recommended for low responders. [Updated]	Conditional	⊕◯◯◯
60	Double stimulation can be considered for urgent fertility preservation cycles. [2019]	GPP	
61	Double stimulation can be used with the intention to accumulate oocytes or embryos when fresh transfer is not planned. [Updated]	Strong	⊕⊕◯◯

Part D: Fertility preservation and oocyte donation

Fertility preservation for patients facing gonadotoxic treatment

62	For patients facing gonadotoxic treatment, ovarian stimulation for fertility preservation should be started irrespective of the menstrual cycle phase. [updated]	Strong	⊕◯◯◯
63	For ovarian stimulation in women seeking fertility preservation for medical reasons the GnRH antagonist protocol is recommended. [2019]	Strong	⊕◯◯◯
64	In ovarian stimulation for fertility preservation in oestrogen sensitive diseases the concomitant use of anti-oestrogen therapy, such as letrozole or tamoxifen, can be considered. [2019]	GPP	
65	For final oocyte maturation in patients facing gonadotoxic treatment, GnRH agonist is preferred. [2025]	GPP	

Elective oocyte cryopreservation

66	Ovarian stimulation for elective oocyte preservation can be started irrespective of the menstrual cycle phase. [2025]	Conditional	⊕◯◯◯
67	GnRH antagonist or progestin protocol are probably recommended over GnRH agonist protocols for pituitary suppression in elective oocyte cryopreservation. [2025]	Conditional	⊕◯◯◯
68	For final oocyte maturation in elective oocyte cryopreservation, GnRH agonist is preferred. [2025]	GPP	

Oocyte donation

69	Conventional follicular start or random-start ovarian stimulation are equally recommended for oocyte donation cycles. [2025]	Strong	⊕◯◯◯
70	If random-start ovarian stimulation is used, oocyte donors need to adopt contraceptive measures to prevent the possibility of a natural pregnancy. [2025]	GPP	
71	Any type of contraception (hormonal, non-hormonal, oral, vaginal or intrauterine) can be used before initiation of ovarian stimulation in oocyte donors.[2025]	GPP	
72	Progestin or intrauterine contraception can be used during ovarian stimulation in oocyte donors. [2025]	GPP	
73	For pituitary suppression in oocyte donors the GnRH antagonist and progestin protocol are probably equally recommended. [2025]	Conditional	⊕⊕◯◯

74	A GnRH agonist protocol for pituitary suppression is not recommended in oocyte donors. [2025]	GPP	
75	The use of recombinant human FSH (r-hFSH), purified FSH, long-acting r-hFSH or hMG is probably equally recommended in oocyte donors undergoing ovarian stimulation. [2025]	Conditional	⊕◯◯◯
76	Gonadotropin dose should be individualised based on ovarian reserve with the goal to maintain donors' safety and also obtain an optimal number of oocytes. [2025]	GPP	
77	The routine use of a GnRH agonist trigger is recommended in oocyte donors using the GnRH antagonist or progestin protocols for pituitary suppression. [2025]	Strong	⊕⊕◯◯
78	The use of a hCG trigger is not routinely recommended in oocyte donation cycles. [2025]	Strong	⊕⊕◯◯

Part E: Monitoring

Hormonal assessment during ovarian stimulation

79	The addition of oestradiol measurements to ultrasound monitoring is probably not recommended. [2019]	Conditional	⊕⊕◯◯
80	The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring is probably not recommended. [2019]	Conditional	⊕◯◯◯

Endometrial thickness

81	Routine monitoring of endometrial thickness during controlled ovarian stimulation is probably not recommended. [2019]	Conditional	⊕◯◯◯
82	The guideline group suggests performing a single measurement of the endometrium during ultrasound assessment on the day of triggering or oocyte pick-up to counsel patients on potential lower pregnancy chance. [2019]	GPP	

Criteria for triggering

83	The association of follicle size as a triggering criterion with outcome has not been sufficiently studied. Physicians may choose the follicle size upon which final oocyte maturation is triggered on a case to case basis. [2019]	Conditional	⊕⊕◯◯
84	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, embryo transfer strategy, 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 16-22 mm. [reworded]	GPP	
85	The GDG does not recommend to base timing of final oocyte maturation triggering on oestradiol levels alone. [2019]	GPP	
86	The GDG does not recommend to base timing of final oocyte maturation on oestradiol/follicle ratio alone. [2019]	GPP	

Hormonal assessment on the day of final oocyte maturation

87	It is probably recommended to measure serum progesterone levels on the day of final oocyte maturation in cycles aimed for a fresh embryo transfer. [2025]	Conditional	⊕◯◯◯	
88	If serum progesterone levels are high, the patient should be counselled about potentially lower ongoing pregnancy/live birth rates. The decision to defer embryo transfer should include other factors (number of oocytes, number of embryos, and embryo quality). [2025]	GPP		
89	It is not recommended to routinely measure serum oestradiol levels on the day of hCG trigger in ovarian stimulation cycles with an intent for a fresh embryo transfer. [2025]	Strong	⊕◯◯◯	
90	It is not recommended to measure serum LH levels on the day of hCG trigger in ovarian stimulation cycles aimed for a fresh embryo transfer. [2025]	Strong	⊕◯◯◯	
91	It is not recommended to measure serum oestradiol, progesterone or luteinizing hormone levels on the day of a GnRH agonist trigger in freeze-all cycles. [2025]	Strong	⊕◯◯◯	

Criteria for cycle cancellation

92	A low response to ovarian stimulation alone is not a reason to cancel a cycle. [2019]	Strong	⊕◯◯◯	
93	The physician should counsel the individual unexpected low responder regarding pregnancy prospects and decide individually whether to continue this cycle. [Updated]	GPP		
94	In GnRH agonist cycles with an ovarian response of ≥19 follicles of ≥11 mm, there is an increased risk of OHSS and preventative measures are recommended, which should include primarily cancelling final oocyte maturation trigger. [Updated]	Strong	⊕◯◯◯	
95	In GnRH antagonist cycles, withholding GnRH agonist triggering may still be considered in women with extremely high ovarian response. [2025]	GPP		

Part F: Triggering ovulation and luteal support

Triggering of final oocyte maturation

96	The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation in ovarian stimulation protocols. [2019]	Strong	⊕⊕◯◯	SoF table 29
97	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. [2019]	Conditional	⊕◯◯◯	
98	It is not recommended to administer recombinant human LH for triggering final oocyte maturation. [2019]	Strong	⊕◯◯◯	SoF table 30
99	The use of GnRH agonist for final oocyte maturation is not recommended in the general IVF/ICSI population with fresh transfer, regardless of luteal phase support (with or without LH-activity). [updated]	Strong	⊕⊕◯◯	SoF table 31

100	If the GnRH agonist trigger with triptorelin is applied, dosages ranging between 0.1-0.4 mg can be chosen. [2019]	GPP		
101	The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for predicted normal responders. [2019]	Conditional	⊕⊕◯◯	SoF table 32 a,b
102	The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for low responders. [2025]	Conditional	⊕⊕◯◯	SoF table 32 c
/	There is too limited evidence to draw conclusions on the use of double trigger for final oocyte maturation for IVF/ICSI.	/	/	Conclusion SoF table 33

Luteal phase support

103	Progesterone is recommended for luteal phase support after IVF/ICSI. [2019]	Strong	⊕◯◯◯	SoF table 34
104	Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used. [2019]	GPP		
105	The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 mg once daily for intramuscular progesterone 25 mg once daily for subcutaneous 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. [2019]	GPP		SoF table 35 a,b,c,d
106	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. [2019]	GPP		SoF table 36 a,b,c
107	Progesterone support should be administered until at least the day of the pregnancy test. [2019]	GPP		SoF table 37
108	Dydrogesterone is probably recommended for luteal phase support. [2019] *There are reports on a relation between dydrogesterone exposure and the occurrence of congenital malformations. These observed relations cannot be translated into a conclusion on causality, and therefore are considered as potential associations.*	Conditional	⊕⊕⊕◯	SoF table 38
109	The addition of oestradiol to progesterone for luteal phase support is probably not recommended. [2019]	Conditional	⊕⊕◯◯	SoF table 39
110	In hCG triggered ovarian stimulation cycles, hCG as luteal phase support in standard dosages of 1500 IU is not recommended. [updated]	Strong	⊕⊕◯◯	SoF table 40 a,b
111	A GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. [updated]	Conditional	⊕⊕◯◯	SoF table 41
112	Repeated GnRH agonist injections, alone or in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. [reworded]	Conditional	⊕◯◯◯	SoF table 42

113	Addition of LH to progesterone for luteal phase support can only be used in the context of a clinical trial. [2019]	Research only		SoF table 43
Part G: Prevention of OHSS				
114	A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS combined with a freeze-all strategy to minimise the risk of severe OHSS. [updated]	Strong	⊕◯◯◯	SoF table 44 a,b,c
115	If a GnRH agonist protocol with hCG trigger is used in high responders, a freeze-all strategy is recommended to decrease the risk of late-onset OHSS. [updated]	GPP		
116	The addition of hCG to GnRH agonist as a dual trigger for final oocyte maturation is probably not recommended for high responders. [2025]	Conditional	⊕◯◯◯	
117	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. [2019]	Conditional	⊕◯◯◯	
118	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. [2019]	GPP		
119	Dopamine agonists are recommended to decrease the risk of early OHSS, particularly in patients receiving hCG for final oocyte maturation. [2025]	Strong	⊕⊕◯◯	SoF table 45
120	A freeze-all strategy is recommended to minimise the risk of late-onset OHSS. [updated]	Strong	⊕⊕◯◯	SoF table 46
121	Prior to start of ovarian stimulation, a risk assessment for high response is advised with the purpose of applying personalised treatment choices on pituitary suppression protocol, FSH dosage, final oocyte maturation trigger and embryo transfer strategy. [updated]	GPP		

PART A: Pre-stimulation evaluation

1. Ovarian response prediction

PICO Question: Is the assessment of the predicted response to ovarian stimulation sufficiently reliable?

Implications following the prediction of an extreme ovarian response is relevant for both the clinicians and patients. Clinicians may suggest personalizing the treatment based on that prediction, and such strategies will be discussed elsewhere in this guideline. For the patients, ovarian response prediction provides information about the chances of success, the safety risks and complications.

Antral follicle count (AFC)

Evidence

A high number of studies have investigated the role of AFC in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and the definition of low and high response has not been uniform. AFC has been studied in GnRH agonist and antagonist cycles and in patients stimulated with different dosages and protocols of follicle stimulating hormone (FSH). Also, several narrative reviews and meta-analyses have been conducted on the subject.

A systematic review and meta-analysis[1] investigated the performance of the AFC to predict a high (6 studies) and low (15 studies) response to ovarian stimulation (Liu et al., 2023). To predict high response, the overall pooled sensitivity of AFC was 0.83 (95% CI 0.77-0.87) and pooled specificity 0.78 (95% CI 0.64-0.88). High heterogeneity was present. The AUC for the predictive value of AFC for a high response to ovarian stimulation was 0.87 (95% CI 0.84-0.89). To predict low ovarian response, the overall pooled sensitivity was 0.75 (95% CI 0.67-0.81) and pooled specificity was 0.82 (95% CI 0.76-0.87). Again, high heterogeneity was found for both. The AUC for the predictive value of AFC for a low response to ovarian stimulation was 0.85 (95% CI 0.82-0.88).

Several studies were identified assessing the predictive accuracy for AFC in ovarian response prediction which were not included in the meta-analysis or were published afterwards, which show similar results to the meta-analysis (Arce et al., 2013, Bancsi et al., 2002, Elgindy et al., 2008, Hochberg et al., 2024, Jayaprakasan et al., 2009, Khairy et al., 2008, Kwee et al., 2007, Lan et al., 2013, Lee et al., 2020, Oehninger et al., 2015, Penarrubia et al., 2010, Sun et al., 2022, Tsakos et al., 2014, Wang et al., 2021).

[1] The IPD meta-analyses by Broer et al 2013a and b are replaced by a more recent meta-analysis. The cohort studies by Bancsi *et al.*, 2004, Jayaprakasan *et al.*, 2010, Mutlu *et al.*, 2013, Soldevila *et al.*, 2007, Tolikas *et al.*, 2011 are included in the meta-analysis.

Table 1: Accuracy of AFC in predicting ovarian response.

AFC		High ovarian response		Low ovarian response		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**	**Remark**
Liu 2023	7190		0.90		0.87	
Other studies:						
Hochberg 2024	4220	≥15 oocytes	0.80			
Sun 2022	2585	>15 oocytes	0.73	≤3 oocytes	0.92	
Wang 2021	84884			≤3 oocytes	0.84	
Lee 2020	263	≥ 20 oocytes	0.81	< 4 oocytes	0.82	
Oehninger 2015	686	>18 oocytes	0.88	<6 oocytes	0.88	
Tsakos 2014	105	>12 oocytes	0.86	<4 oocytes	0.86	
Lan 2013	382	>20 oocytes	0.81	≤3 oocytes	0.80	
Arce 2013	375	≥15 oocytes	0.64	≤3 oocytes	0.74	r-hFSH stimulation
Arce 2013	374	≥15 oocytes	0.65	≤3 oocytes	0.67	hMG stimulation
Penarrubia 2010	98			≤3 oocytes	0.90	
Jayaprakasan 2009	141			<4 oocytes	0.89	
Khairy 2008	148			<4 oocytes	0.79	
Elgindy 2008	33			<4 oocytes	0.94	
Kwee 2007	110	>20 oocytes	0.92	<6 oocytes	0.83	
Bancsi 2002	120			<4 oocytes	0.87	

Conclusion

The prediction of ovarian response categories by AFC alone is reliable.

ANTI-MÜLLERIAN HORMONE (AMH)

Evidence

A high number of studies have investigated the role of AMH in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and studies have used different assays for the measurement of the AMH values. AMH has been studied in GnRH agonist and antagonist cycles and in patients stimulated with different dosages and protocols of FSH. Moreover, the definition of a low and high response has not been uniform, which nevertheless showed AMH to be a good predictor of ovarian response. Several narrative reviews have been written next to different meta-analyses on the subject.

A systematic review and meta-analysis[2] investigated the performance of AMH to predict a high (13 studies) and low (29 studies) response to ovarian stimulation (Liu et al., 2023). To predict high response, the overall pooled sensitivity of AMH was 0.79 (95% CI 0.74-0.83) and pooled specificity 0.79 (95% CI 0.74-0.83). The AUC for the predictive value of AMH for a high response to ovarian stimulation was 0.86 (95% CI 0.82-0.89). To predict low ovarian response, the overall pooled sensitivity was 0.78 (95% CI

[2] The IPD meta-analyses by Broer et al 2013a and b are replaced by a more recent meta-analysis. The cohort studies by Heidar *et al.*, 2015, Jayaprakasan *et al.*, 2010, Li *et al.*, 2016, Mutlu *et al.*, 2013, Tolikas *et al.*, 2011 are included in the meta-analysis.

0.74-0.80) and pooled specificity was 0.79 (95% CI 0.76-0.83). High heterogeneity was found for both. The AUC for the predictive value of AMH for a low response to ovarian stimulation was 0.85 (95% CI 0.81-0.88).

Several studies were identified assessing the predictive accuracy for AMH in ovarian response prediction which were not included in the meta-analysis or were published afterwards, which show similar results (Andersen et al., 2011, Arce et al., 2013, Bosch et al., 2023, Elgindy et al., 2008, Hochberg et al., 2024, Huang et al., 2019, Lan et al., 2013, Lee et al., 2020, Oehninger et al., 2015, Sun et al., 2022, Tsakos et al., 2014).

Table 2: Accuracy of AMH in predicting ovarian response.

AMH		**High ovarian response**		**Low ovarian response**		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**	**Remark**
Liu 2023	7190		0.89		0.87	
Other studies:						
Hochberg 2024	4220	≥15 oocytes	0.71			
Bosch 2023	1248	>15 oocytes	0.89	≤3 oocytes	0.85	
Sun 2022	2585	>15 oocytes	0.73	≤3 oocytes	0.79	
Wang 2021	41702			≤3 oocytes	0.86	
Lee 2020	263	≥ 20 oocytes	0.80	< 4 oocytes	0.85	
Huang 2019	523	>15 oocytes	0.77	< 4 oocytes	0.86	
Oehninger 2015	686	>18 oocytes	0.86	<6 oocytes	0.87	
Tsakos 2014	105	>12 oocytes	0.66	<4 oocytes	0.63	
Arce 2013	374	≥15 oocytes	0.77	≤3 oocytes	0.78	hMG stimulation
Arce 2013	375	≥15 oocytes	0.81	≤3 oocytes	0.90	r-hFSH stimulation
Lan 2013	382	>20 oocytes	0.76	≤3 oocytes	0.88	
Andersen 2011	442	>18 oocytes	0.77	<6 oocytes	0.84	
Elgindy 2008	33			<4 oocytes	0.90	

Conclusion

The prediction of ovarian response categories by AMH alone is reliable.

Basal Follicle Stimulating Hormone (FSH)

Evidence

A high number of studies have investigated the role of basal FSH levels in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and the definition of a low and high response has not been uniform. Also, several narrative reviews and meta-analyses have been conducted on the subject.

An individual patient data (IPD) meta-analysis assessed the accuracy of basal FSH and reported moderate accuracy of basal FSH in predicting both a low response (ROC-AUC of 0.66 (95% CI 0.62-0.69) and an excessive response (ROC-AUC of 0.64 (95% CI 0.61-0.67)) (Broer et al., 2013a, Broer et al., 2013b).

Several studies were identified assessing the predictive accuracy for basal FSH in ovarian response prediction which were not included in the IPD meta-analysis or were published afterwards, which show similar results to the IPD meta-analyses (Arce et al., 2013, Bancsi et al., 2002, Elgindy et al., 2008, Jayaprakasan et al., 2009, Khairy et al., 2008, Kwee et al., 2007, Lee et al., 2020, Mutlu et al., 2013, Oehninger et al., 2015, Penarrubia et al., 2010, Soldevila et al., 2007, Tolikas et al., 2011, Tsakos et al., 2014, Wang et al., 2021).

Table 3: Accuracy of basal FSH in predicting ovarian response.

basal FSH		**High ovarian response**		**Low ovarian response**		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**	**Remark**
Broer 2013a/b	4786/5705	>15 oocytes	0.64	≤4 oocytes	0.66	
Other studies:						
Wang 2021	85052			≤3 oocytes	0.69	
Lee 2020	263	≥ 20 oocytes	0.63	< 4 oocytes	0.73	
Oehninger 2015	686	>18 oocytes	0.88			
Tsakos 2014	105	>12 oocytes	0.72	<4 oocytes	0.67	
Arce 2013	374	≥15 oocytes	0.71	≤3 oocytes	0.73	hMG stimulation
Arce 2013	375	≥15 oocytes	0.73	≤3 oocytes	0.72	r-hFSH stimulation
Mutlu 2013	192			<4 oocytes	0.75	
Tolikas 2011	90			<4 oocytes	0.65	
Penarrubia 2010	98			≤3 oocytes	0.62	
Jayaprakasan 2009	141			<4 oocytes	0.69	
Elgindy 2008	33			<4 oocytes	0.85	
Khairy 2008	148			<4 oocytes	0.69	
Kwee 2007	110	>20 oocytes	0.80	<6 oocytes	0.83	
Soldevila 2007	327			≤5 oocytes	0.63	
Bancsi 2002	120			<4 oocytes	0.84	

Conclusion

The prediction of ovarian response categories by basal FSH alone is not sufficiently reliable, compared to the predictive accuracy by the AFC and AMH.

INHIBIN B

Evidence

A high number of studies have investigated the role of inhibin B in the prediction of ovarian response to ovarian stimulation. In 2006, a systematic review and meta-analysis (9 studies, 788 cycles) has been performed including inhibin B (Broekmans et al., 2006). Although variations between studies regarding definition of poor response, study quality and study characteristics existed, statistical analysis showed these not related to the predictive performance of inhibin B. The sensitivity of inhibin B in the prediction of a poor response ranged from 32 to 89%, the specificity ranged from 29 to 95%. The spearman correlation coefficient for sensitivity and specificity was -0.93. From logistic regression the pre- and post-test probabilities of a poor response were calculated. These demonstrated that inhibin B has a modest accuracy in the prediction of a poor response (Broekmans et al., 2006).

Since the publication of this meta-analysis a few more studies have been published assessing the predictive accuracy for inhibin B in ovarian response prediction (Arce et al., 2013, Fawzy et al., 2002, Hendriks et al., 2005, Kwee et al., 2007, Penarrubia et al., 2010, van Rooij et al., 2002).

Table 4: Accuracy of Inhibin B in predicting ovarian response.

Inhibin B		**High ovarian response**		**Low ovarian response**		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**	**Remark**
Arce 2013	374	≥15 oocytes	0.60	≤3 oocytes	0.62	hMG stimulation
Arce 2013	375	≥15 oocytes	0.53	≤3 oocytes	0.64	r-hFSH stimulation
Penarrubia 2010	98			≤3 oocytes	0.61	
Kwee 2007	110	>20 oocytes	0.93	<6 oocytes	0.86	for the increment of inhibin B in the EFORT
Hendriks 2005	63			<4 oocytes	0.76	
Fawzy 2002	54			<8 MII oocytes	0.96	
Van Rooij 2002	119			<4 oocytes	0.76	

EFORT: Exogenous follicle stimulating hormone ovarian reserve test

Conclusion

The prediction of ovarian response categories by inhibin B alone is not sufficiently reliable.

BASAL OESTRADIOL

Evidence

Basal oestradiol has also been studied as a predictor of ovarian response to ovarian stimulation. The systematic review by Broekmans *et al.*, mentioned before, also investigated the performance of basal oestradiol in predicting ovarian response (10 studies, 3911 women) (Broekmans et al., 2006). The sensitivity of basal oestradiol in the prediction of a poor response ranged from 3 to 83%, the specificity ranged from 13 to 98%. The spearman correlation coefficient for sensitivity and specificity was -0.50. From likelihood ratio (LR) the pre- and post-test probability of a poor response was calculated. This demonstrated that basal oestradiol has a low accuracy in the prediction of a poor response (Broekmans et al., 2006).

Since the publication of this meta-analysis, a few more studies have been published assessing the predictive accuracy for basal oestradiol in ovarian response prediction (Hendriks et al., 2005, Khairy et al., 2008, Kwee et al., 2007, Lee et al., 2020, Penarrubia et al., 2010, van Rooij et al., 2002). These have confirmed the low accuracy of basal oestradiol.

Table 5: Accuracy of basal oestradiol in predicting ovarian response.

basal estradiol		High ovarian response		Low ovarian response		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**	**Remark**
Lee 2020	263	≥ 20 oocytes	0.52	< 4 oocytes	0.66	
Penarrubia 2010	98			≤3 oocytes	0.55	
Khairy 2008	148			<4 oocytes	0.51	
Kwee 2007	110	>20 oocytes	0.83	<6 oocytes	0.75	for the increment of basal oestradiol in the EFORT
Hendriks 2005	63			<4 oocytes	0.54	
Van Rooij 2002	119			<4 oocytes	0.52	

EFORT: Exogenous follicle stimulating hormone ovarian reserve test

Conclusion

Basal oestradiol alone is not a predictor of ovarian response.

BASAL PROGESTERONE

Evidence

No studies were retrieved investigating the role of basal progesterone in the prediction of ovarian response to ovarian stimulation in terms of sensitivity, specificity and AUC.

BASAL LH

Evidence

No studies were retrieved investigating the role of basal LH in the prediction of ovarian response to ovarian stimulation in terms of sensitivity, specificity and AUC.

AGE

Evidence

A high number of studies have investigated the role of age in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and the definition of low and high response has not been uniform. However, all these studies show an unsatisfactory ROC curve for age as predictor of ovarian response. Several meta-analyses have been conducted on the subject.

The IPD meta-analyses mentioned earlier also assessed the accuracy of age and reported a limited accuracy of age alone in predicting both a poor response (ROC-AUC of 0.60 (95% CI 0.57-0.64)) and an excessive response (ROC-AUC of 0.61 (95% CI 0.58-0.64)) (Broer et al., 2013a, Broer et al., 2013b).

Several studies were identified assessing the predictive accuracy for age in ovarian response prediction which were not included in the IPD meta-analysis or were published afterwards (Bancsi et al., 2002, Jayaprakasan et al., 2009, Khairy et al., 2008, Kwee et al., 2007, Lee et al., 2020, Mutlu et al., 2013, Oehninger et al., 2015, Penarrubia et al., 2010, Wang et al., 2021).

Table 6: Accuracy of age in predicting ovarian response.

Age		High ovarian response		Low ovarian response	
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**
Broer 2013a/b	4786/5705	>15 oocytes	0.61	≤4 oocytes	0.60
Other studies:					
Sun 2022	2585	>15 oocytes	0.65	≤3 oocytes	0.75
Wang 2021	88987			≤3 oocytes	0.72
Lee 2020	263	≥ 20 oocytes	0.65	< 4 oocytes	0.68
Oehninger 2015	686	>18 oocytes	0.55	<6 oocytes	0.55
Mutlu 2013	192			<4 oocytes	0.76
Penarrubia 2010	98			≤3 oocytes	0.75
Jayaprakasan 2009	141			<4 oocytes	0.74
Khairy 2008	148			<4 oocytes	0.71
Kwee 2007	110	>20 oocytes	0.71	<6 oocytes	0.63
Bancsi 2002	120			<4 oocytes	0.61

Conclusion

The prediction of ovarian response categories by age alone is not sufficiently reliable.

BODY MASS INDEX (BMI)

Evidence

With the growing interest for ovarian response prediction, the role of BMI in ovarian response has been questioned. However, there are only a few studies actually assessing the accuracy of BMI as a predictor of ovarian response. In these studies, BMI was found to have a small to no predictive accuracy for ovarian response to ovarian stimulation.

The IPD meta-analyses mentioned earlier also assessed the accuracy of BMI and concluded that BMI was not a significant predictor of ovarian response, neither for poor nor a high response (Broer et al., 2013a, Broer et al., 2013b).

Table 7: Accuracy of BMI in predicting ovarian response.

BMI		High ovarian response		Low ovarian response	
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**
Broer 2013a/b	4786/5705	>15 oocytes		≤4 oocytes	
Other studies:					
Sun 2022	2585	>15 oocytes	0.51	≤3 oocytes	0.58
Lee 2020	263	≥ 20 oocytes	0.52	< 4 oocytes	0.54
Khairy 2008	148			<4 oocytes	0.68

Conclusion

BMI alone is not a predictor of ovarian response.

OVERALL RECOMMENDATION

Evidence

Based on the available evidence both AFC and AMH show a high accuracy in the predication of a low and high response (Table 1 and 2). The accuracy of Basal FSH and Inhibin B levels is moderate (Table 3 and 4). Basal oestradiol, age and BMI are not good predictors of ovarian response to hyperstimulation (Table 5, 6 and 7).

Recommendation

For predicting high and low response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended. [updated]	Strong	⊕○○○

Age, BMI, basal FSH, inhibin B, basal oestradiol, basal progesterone and basal LH are not recommended for the prediction of ovarian response. [2025]	Strong	⊕○○○

Justification

AFC and AMH both have a high accuracy in the prediction of ovarian response category (high or low). Taking into account false positive and negative rate of the test it may be recommended for clinical application. The clinician can decide which test is most appropriate for their clinical setting.

In this guideline, we did not compare AMH and AFC with each other nor studied the added effect of using both tests for ovarian response prediction. However, the IPD meta-analysis did demonstrate that these tests do have added value to female age alone. Moreover, there was no difference in the performance of these tests and combining them did not improve the prediction of ovarian response (Broer et al., 2013a, Broer et al., 2013b).

Basal FSH and inhibin B do have some predictive value for ovarian response, however for an accurate prediction very high cut-off levels need to be used. This implies that only very few women will have such an abnormal FSH or Inhibin B test results. This results in hardly any clinical value, especially since there are other tests available with a higher accuracy. Age also has some predictive value, however assessment of ovarian response category by age alone is not sufficiently reliable. Basal oestradiol and BMI alone are not predictors of ovarian response. Therefore, we recommend not using basal FSH, inhibin B, basal oestradiol, age or BMI for the prediction of ovarian response.

As all original studies have been performed using different assays or ranges for AFC and AMH, it is not possible to combine these data to calculate cut-offs for the prediction of a low or high response. Regarding the use of AMH and AFC for individualised gonadotropin dose selection, the reader is referred to the Cochrane review by Lensen *et al.* since this was not investigated in this guideline (Lensen et al., 2017).

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2. Pregnancy prediction

PICO Question: What is the prognostic value of hormonal assessment at baseline?

Antral follicle count (AFC)

Evidence

In an IPD meta-analysis, including 55 study reports, AFC had no predictive effect for ongoing pregnancy after IVF (AUC 0.50, 95% CI 0.40-0.59) (Broer et al., 2013).

Conclusion

AFC alone is not a predictor for the outcome pregnancy.

Anti-Müllerian hormone (AMH)

Evidence

In an IPD meta-analysis, including 55 study reports, AMH had only a very low predictive value for ongoing pregnancy after IVF (AUC 0.55, 95% CI 0.45-0.64) (Broer et al., 2013).

In a prospective cohort study, the relationship between AMH levels and pregnancy outcomes was investigated in 50 patients undergoing ovarian stimulation for IVF/ICSI (Umarsingh et al., 2020). The studied population was divided into low to normal AMH (0.3-0.9 ng/mL; n=3), normal AMH (<1 ng/mL; n=17) and high AMH (<3 ng/mL; n=22). Pregnancy rates were 27.3% (6/22) in the high AMH group, 35.3% (6/17) in the normal AMH group and 0% (0/3) in the low to normal AMH group. AUC to predict pregnancy outcomes of AMH was 0.497.

In a prospective cohort study, the possible association between AMH and clinical outcomes in IVF cycles was investigated in 124 patients undergoing their first ovarian stimulation cycle (Li et al., 2015). No direct correlation was observed between serum AMH and inhibin B levels on day 2/3 and clinical pregnancy.

In a prospective cohort study, it was investigated if AMH level on day 3 could predict reproductive outcomes in 164 women with PCOS undergoing their first IVF treatment cycle (Xi et al., 2012). The study population was divided into low AMH (≤4.85 ng/mL; n=41), average AMH (4.85-8.82 ng/mL; n=82) and high AMH (≥8.82 ng/mL; n=41). No significant difference in clinical pregnancy rate was observed with low, average, or high AMH (65% (26/40) vs. (66.7% (50/75) vs. 45.9% (17/37)).

In a prospective cohort study, the possible relationship between AMH levels on day 3 and reproductive outcomes was investigated in 60 women with PCOS (80 cycles) (Kaya et al., 2010). The studied population was divided according to the <25th (21 cycles), 25-75 (39 cycles) and >75th percentile (20 cycles) of serum AMH on day 3. The clinical pregnancy rate increased significantly with AMH levels (33.3% (7/21) vs. 46.1% (19.39) vs. 60% (12/20)). For predicting clinical pregnancy rates, using a cutoff value of 3.2 ng/mL, the sensitivity was 72.7% and the specificity 77.3%.

Conclusion

AMH alone is not a predictor of the outcome pregnancy.

Basal Follicle Stimulating Hormone (FSH)

Evidence

In an IPD meta-analysis, including 55 study reports, basal FSH had only a very low predictive value for ongoing pregnancy after IVF (AUC 0.53, 95% CI 0.43-0.62) (Broer et al., 2013).

In a large retrospective cohort study, including 19682 cycles, the relationship between early follicular FSH levels and oestradiol levels and reproductive outcomes was investigated (Frazier et al., 2004). In the final model for live birth delivery, statistically significant negative predictors included increasing age, elevated FSH ratio, elevated oestradiol ratio.

Conclusion

Basal FSH alone is not a predictor of the outcome pregnancy.

Inhibin B

Evidence

In a systematic review and meta-analysis, including 3 study reports, ROC curves were estimated for the predictive accuracy of inhibin B for non-pregnancy (Broekmans et al., 2006). Extreme threshold levels were necessary to obtain a modest positive likelihood ratio of ~4–5, resulting in a post-test pregnancy rate of approximately 5%. Such abnormal test results occur only in a very limited number of patients.

In a prospective cohort study, the possible association between AMH and clinical outcomes in IVF cycles was investigated in 124 patients undergoing their first ovarian stimulation cycle (Li et al., 2015). No direct correlation was observed between inhibin B levels on day 2/3 and clinical pregnancy.

Conclusion

Inhibin B alone is not a predictor of the outcome pregnancy.

Basal oestradiol

Assessment of oestradiol at initiation of stimulation is frequently performed in IVF/ICSI and an elevated level usually signifies the presence of a simple follicular cyst, which is then confirmed at ultrasound. However, prediction of the outcome of stimulation has also been attempted using E2 level at initiation of stimulation.

Evidence

In a systematic review and meta-analysis, including 9 study reports, ROC curves were estimated for the predictive accuracy of oestradiol for non-pregnancy (Broekmans et al., 2006). For prediction of non-pregnancy no clear threshold levels could be identified for that would lead to an adequate combination of LR, post-test probability and abnormal test rate.

In a large retrospective cohort study, including 19682 cycles, the relationship between early follicular FSH levels and oestradiol levels and reproductive outcomes was investigated (Frazier et al., 2004). In the final model for live birth delivery, statistically significant negative predictors included the combination of increasing age, elevated FSH ratio, elevated oestradiol ratio.

One retrospective study in patients with unexplained infertility undergoing ovarian stimulation and intercourse shows a significantly lower chance of pregnancy in women with higher oestradiol levels at initiation of stimulation (Costello et al., 2001).

Conclusion

Oestradiol alone is not a predictor of the outcome pregnancy.

BASAL PROGESTERONE

In a proportion of cycles, progesterone remains elevated at menstruation. Elevated progesterone levels at the intended starting date of ovarian stimulation could be associated with reduced pregnancy rates. The proportion of patients with progesterone levels >1.6 ng/ml on cycle day 2 was 4.9% (95% CI 3.2-7.4) in a cohort study by Kolibianakis *et al.* (2004) and 6.2% (95% CI 4-9) in a cohort study by Blockeel *et al.* (Blockeel et al., 2011, Kolibianakis et al., 2004). A more recent study by Hamdine *et al.* reported 13.3% (95% CI 8-20) of patients with progesterone levels >1.5 ng/ml. Faulisi *et al.* reported 0.3% (95% CI 0.01-1.15) of patients with progesterone levels >1.6 ng/ml on cycle day 3 (Faulisi et al., 2017, Hamdine et al., 2014). Due to the low incidence it seems unnecessary to evaluate this research question for progesterone levels >1.6 ng/ml on cycle day 3.

Evidence

A meta-analysis[3], including 3 cohort studies and 773 women, investigated the effect of elevated progesterone levels at baseline on reproductive outcomes (Lim et al., 2024). No significant difference was found for live birth rate with elevated progesterone levels at baseline at threshold level >1.5 ng/mL (OR 0.76, 95% CI 0.39–1.49, 2 studies, N=309). Similarly, no significant difference was found for clinical pregnancy rate at threshold level >0.65 ng/mL (OR 1.41, 95% CI 0.93–2.13, 1 study, n=464) or threshold level >1.5 ng/mL (OR 0.81, 95% CI 0.38-1.71, 2 studies, n=309).

A retrospective cohort study (418 women, 461 cycles) reported lower live birth rates of 18.2% (2/11) and 16.7% (1/6) with progesterone < or >1.5 ng/mL on hCG day respectively, in patients with elevated (>1.5 ng/mL) levels at the start of ovarian stimulation, compared to 33.8% in controls (progesterone <1.5 ng/mL both at the start of OS and on hCG day) (Panaino et al., 2017).

Fausili *et al.* showed that progesterone assessment on day 3 of stimulation is inaccurate in predicting clinical pregnancy (ROC-AUC 0.54, 95%CI 0.47-0.61) (Faulisi et al., 2017).

Conclusion

Assessment of progesterone prior to initiation of stimulation on cycle day 2 in women undergoing ovarian stimulation with GnRH antagonist and gonadotrophins may be beneficial to identify cases

[3] The meta-analysis by Hamdine *et al.*, 2014 cited here in the 2019 version of the guideline was replaced by a more recent meta-analysis.

with a lower than normal probability of pregnancy. The currently available evidence, however, is not solid, and the clinical value of this test was not assessed.

Baseline LH

Evidence

In a retrospective cohort study, the effect of elevated basal LH levels on reproductive outcomes was investigated in poor, normal and high responders (Zhang et al., 2024). Women were divided in two groups based on their baseline LH levels: <5 IU/L and ≥5 IU/L. OHSS rate was significantly lower in poor responders with low baseline LH levels (0% (0/270) vs. 2.6% (4/157). No significant difference in OHSS was observed for normal and high responders with LH levels below or above the threshold of 5 IU/L. No significant difference in clinical pregnancy rates were observed in poor responders (50.0% (134/270) vs. 47.8% (75/157), normal responders (58.0% (196/338) vs. 53.5% (124/232) or high responders (59.6% (87/146) vs. 68.9% (173/251)) with LH levels below or above the threshold.

In a retrospective cohort study, the effect of elevated basal LH levels on reproductive outcomes after IVF/ICSI was assessed in women with PCOS (Liu and Wang, 2023). Women were divided into two groups based on basal LH levels, i.e. high basal LH (LH≥12.455 IU/L; n=59) and low basal LH (LH<12.455 IU/L, n=176). Comparing the results of women with high and low basal LH, no significant difference was observed in cumulative live birth rate (61.82% (34/55) vs. 60% (99/165)) or incidence of OHSS (3.39% (2/59) vs. 1.14% (2/176)).

In a retrospective cohort study, the effect of elevated basal LH levels on reproductive outcomes after IVF/ICSI was assessed in women with PCOS (Wang et al., 2022). Women were divided into three groups based on basal LH, i.e. ≤5 mIU/mL (n=65), 5-10 mIU/mL (n=54) and ≥10 mIU/mL (n=23). Comparing the results of women with ≤5 mIU/mL, 5-10 mIU/mL and ≥10 mIU/mL, no significant differences were found for cumulative live birth rate (23.08% (15/65) vs. 31.48% (17/54) vs. 17.39% (4/23)).

In another retrospective cohort study, the effect of elevated basal LH levels on reproductive outcomes after IVF/ICSI was assessed in women with PCOS (Sun et al., 2018). Women were divided into categories based on basal LH, i.e; < 5 mIU/mL (n=575), between 5 and 7.5 mIU/mL (n=216), between 7.5 and 10 mIU/mL (n=115), and ≥ 10 mIU/mL (n=105). The number of metaphase II oocytes was significantly higher in the group with basal LH≥10 mIU/mL than the groups with basal LH between 7.5 and 10mIU/mL, basal LH between 5 and 7.5 mIU/mL, and basal LH <5 mIU/mL (17.18±9.60 vs. 13.47±9.38 vs. 13.97±8.65 vs. 11.10±7.24). The number of MII oocytes retrieved was positively correlated with the basal LH level (r=0.261). However, no significant difference was seen in clinical pregnancy rates between the different groups of basal LH (47.7% (288/604) vs. 46.5% (112/241) vs. 58.8% (70/119) vs. 55.5% (61/110)).

In a retrospective study, the possible influence of endogenous LH concentrations on ongoing pregnancy rates were investigated (Doody et al., 2010). Patients were stratified into the 25th, 25-75, and 75th percentiles of serum LH concentrations. The ongoing pregnancy rates were not significantly different in women with low, normal or high LH levels on day 1 (36.8% (29.6-44.4) vs. 36.8% (31.7-42.1) vs. 37.9% (30.7-45.6)).

Conclusion

Most studies divided patients into categories based on basal LH levels. However, none of the included studies reported significant differences in the outcome pregnancy across LH level categories.

AGE

Evidence

In an IPD meta-analysis, of all patient characteristics, female age alone was the strongest predictor of ongoing pregnancy (OR 0.94, 95% CI 0.89-0.99) (Broer et al., 2013).

Conclusion

Female age alone is a predictor of the outcome pregnancy.

BODY MASS INDEX (BMI)

Evidence

In an IPD meta-analysis, among patient characteristics, BMI was significantly associated with ongoing pregnancy (OR 0.91, 95% CI 0.85-0.97). In a multivariable model, only BMI added any predictive value to age (Broer et al., 2013).

Conclusion

BMI alone is a predictor of the outcome pregnancy.

OVERALL RECOMMENDATION

Evidence

Based on the available evidence only female age and BMI are predictors of pregnancy and live birth. The accuracy of AFC, AMH, basal FSH, basal LH, basal oestradiol, basal progesterone and inhibin B levels are slight to not predictive for pregnancy and live birth.

Recommendation

AFC, AMH, basal FSH, basal LH, basal oestradiol, basal progesterone and inhibin B are not recommended for the prediction of pregnancy and live birth. [updated]	Strong	⊕◯◯◯

Female age and BMI are predictors of pregnancy and live birth. [2025]	Strong	⊕◯◯◯

Justification

The IPD meta-analysis and the systematic review show that only female age and BMI have predictive value for pregnancy and live birth (Broekmans et al., 2006, Broer et al., 2013). Important to note is that the highest BMI included in the IPD by Broer *et al.* was 30. Still, these results were confirmed by a large meta-analysis of 21 cohort studies, including a total of 682,532 cycles, evaluating the association of female obesity with the probability of live birth following IVF (Sermondade et al., 2019). A negative association was found between obese women and live birth rate after IVF (RR 0.85, 95% CI 0.82-0.87). Subgroup analyses performed according to cycle rank (only first cycle, all cycles, unspecified) or oocyte origin (autologous, oocyte donation, both, unspecified) did not modify the overall interpretation.

Assessment of progesterone prior to initiation of stimulation on cycle day 2 in women undergoing ovarian stimulation with GnRH antagonist and gonadotrophins may be beneficial to identify cases with a lower than normal probability of pregnancy. The currently available evidence, however, is not solid, and the clinical value of this test was not assessed. The necessity of progesterone testing is dubious due to the very low incidence of abnormal test results. Moreover, as a diagnostic test it has no meaningful and evidence-based link to a change of the treatment strategy, in order to undo the potential negative effect on prognosis. Also, cycle cancellation or delaying stimulation initiation has not been shown to improve clinical outcomes. However, since a blood test is required at initiation of stimulation (cycle day 2), progesterone assessment can be incorporated in the patient evaluation prior to FSH administration. The recommendation is not applicable to patients >39 years of age.

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PART B: Pre-treatment therapies

3. Pre-treatment therapies

PICO QUESTION: DOES HORMONE PRE-TREATMENT IMPROVE EFFICACY AND SAFETY OF OVARIAN STIMULATION?

Pre-treatment therapies aim to suppress or to reduce LH and/or FSH secretion prior to gonadotrophin stimulation in IVF cycles. They are used by clinicians for different purposes such as synchronisation of follicular development, prevention of occurrence of early large follicle or spontaneous LH-surge, reduction of cyst formation. Pre-treatment is also used for scheduling IVF cycles for the benefit of clinicians and people in the laboratory as well as patients. It allows to plan IVF activity within weeks and months and to avoid work on weekends and holidays. The use of pre-treatment for scheduling purpose is not addressed in this guideline.

OESTROGEN PRE-TREATMENT

Evidence

A systematic review and meta-analysis[4] compared reproductive outcomes for IVF/ICSI with oestrogen pre-treatment compared to no pre-treatment in the GnRH antagonist protocol (Zhu et al., 2022). No significant difference was found between oestrogen pre-treatment and no pre-treatment in women with a normal response to ovarian stimulation for live birth rate (4 RCTs; OR 0.98; 95% CI 0.74-1.30; 919 women) or ongoing pregnancy rate (7 RCTs; OR 0.92; 95% CI 0.69-1.21; 1236 women).

A recent RCT investigated the use of steroid pre-treatment in IVF/ICSI in the GnRH antagonist protocol in 52 women (Fernández-Prada et al., 2022). Estradiol valerate treatment was started on day 25 of the cycle preceding at a daily dose of 2 mg/12 hours until the day before the start and not beyond 7th day of cycle. No significant difference was found between oestrogen pre-treatment and no pre-treatment for cumulative live birth rate (27.3% (6/22) vs. 47.6% (10/21)), live birth rate (28.6% (4/14) vs. 46.7% (7/15)). There was also no significant difference in the number of MII oocytes between the study and control group (5.76±3.67 vs. 6.15±4.68).

Two RCTs compared oestrogen pre-treatment to no pre-treatment in the GnRH antagonist protocol in women experiencing a low ovarian response to stimulation (Ghasemzadeh et al., 2020, Zhang et al., 2022). In the RCT by Ghasemzadeh *et al.*, oral oestradiol valerate (4 mg) was initiated from the 21st day of the previous IVF cycle, and continued to the second day of the cycle, the day of starting gonadotropin stimulation. No significant differences were found in the number of MII oocytes between oestradiol pre-treatment and no pre-treatment (3.6±0.3 vs. 2.8±0.3) (Ghasemzadeh et al., 2020). In the RCT by Zhang *et* al., estrogen valerate was started on day 7 after ovulation at a dose of 2mg twice a day until day 2 of their next menstruation. No significant difference was found between oestrogen pre-treatment

[4] The Cochrane meta-analysis by Farquhar *et al.*, 2017 was replaced by a more recent systematic review. The RCT by Shahrokh Tehrani Nejad *et al.*, 2018 is included in the meta-analysis and therefore no longer included separately.

and no pre-treatment for clinical pregnancy rate per first transfer (19.3 (23/276) vs. 28.7% (43/276)) or number of MII oocytes (2.9±2.5 vs. 3.1±2.4) (Zhang et al., 2022).

In an RCT, oestrogen pre-treatment was compared to no pre-treatment in the fixed GnRH antagonist protocol for women of advanced age (38-42 years) (Cédrin-Durnerin et al., 2024). Oestradiol pre-treatment started between day 20 and 24 of the previous cycle, until Wednesday evening following the onset of the menses, followed by ovarian stimulation on Friday. No significant differences were found between the pre-treatment and no pre-treatment group for cumulative live birth rate (17.7% (26/147) vs. 22.9% (33/144)), live birth rate per transfer (16.2% (16/147) vs. 18.5% (17/144)) or number of mature oocytes retrieved (7.0±5.5 vs. 7.3±5.2).

Recommendation

Pre-treatment with oestrogen before ovarian stimulation using the GnRH antagonist protocol is not recommended for improving efficacy. [updated]	Strong	⊕⊕◯◯

Justification

There is no evidence of a beneficial effect on live birth rate/ongoing pregnancy rate using oestrogen as pre-treatment in GnRH antagonist protocol, compared to no pre-treatment. These results were confirmed by a more recent network meta-analysis, which also found no significant difference in live birth rate when comparing oestradiol pre-treatment to no pre-treatment in GnRH antagonist protocol only (RR 0.88, 95% CI 0.66-1.16, 3 RCTs, n=585) (Venetis et al., 2023). Due to methodological shortcomings, this network meta-analysis could not be included in the evidence section. The evidence regarding the effect of oestradiol pre-treatment on the number of oocytes retrieved is conflicting.

This recommendation is not restricted to a specific group of women.

PROGESTOGEN PRE-TREATMENT

Evidence

A Cochrane systematic review and meta-analysis investigated the effect of progesterone pre-treatment for OS in 4 RCTs including 421 women. When progestogen pre-treatment was compared with no intervention, there was no difference between the groups in live birth/ongoing pregnancy rate in GnRH agonist protocols (2 RCT, OR 1.35, 95% CI 0.69-2.65, 222 women). There was insufficient evidence to determine whether there was a difference in live birth/ongoing pregnancy rate in the GnRH antagonist protocol (1 RCT, OR 0.67, 95% CI 0.18-2.54, 47 women) (Farquhar et al., 2017).

There was insufficient evidence to determine whether pre-treatment with progestogen resulted in a difference between the groups in the mean number of oocytes retrieved, both in GnRH agonist (MD -0.52, 95%CI -2.07 to 1.02, 2 RCT; and GnRH antagonist protocols (MD 2.70, 95% CI -0.98 to 6.38, 1 RCT) (Farquhar et al., 2017).

Recommendation

Pre-treatment with progesterone before ovarian stimulation is probably not recommended for improving efficacy. [reworded]	Conditional ⊕⊕◯◯

Oestrogen or progesterone pre-treatment can be used for scheduling purposes given the data on efficacy and safety. [reworded]	GPP

Justification

The available evidence indicates no beneficial effect on live birth/ongoing pregnancy rate, using progestogen as pre-treatment in GnRH agonist nor GnRH antagonist protocols. These results were confirmed by a more recent network meta-analysis, which also found no significant difference in live birth rate when comparing progesterone pre-treatment to no pre-treatment in GnRH antagonist protocol only (RR 0.87, 95% CI 0.62 -1.22, 2 RCT, n=416) (Venetis et al., 2023). Due to methodological shortcomings, this network meta-analysis could not be included in the evidence section. There is low quality evidence of an increased clinical pregnancy rate with progestogen pre-treatment in GnRH agonist protocols.

This recommendation is not restricted to a specific group of women, although women with PCOS were excluded from the meta-analysis by Farquhar *et al.* (Farquhar et al., 2017).

COMBINED ORAL CONTRACEPTIVE PILL PRE-TREATMENT

Evidence

A Cochrane systematic and meta-analysis reported that in the GnRH antagonist protocol with COCP pre-treatment (12-28 days), the rate of live birth/ongoing pregnancy was lower than with no pre-treatment (OR 0.74, 95% CI 0.58-0.95, 6 RCT, 1335 women). There was no evidence of a difference between the groups in OHSS rates (OR 0.98, 95% CI 0.28-3.40, 2 RCT, 642 women) or number of oocytes (MD 0.44, 95% CI -0.11 to 0.99, 6 RCT) (Farquhar et al., 2017). In a subgroup of poor responders (80 women) there was no difference for live birth/ongoing pregnancy rate (OR 1.71, 95% CI 0.61-4.79, 1 RCT) or number of oocytes (MD 0.70, 95% CI -0.11 to 1.51, 1 RCT) (Farquhar et al., 2017, Kim et al., 2011).

A recent RCT investigated the use of steroid pre-treatment in IVF/ICSI in a GnRH antagonist protocol in 52 women (Fernández-Prada et al., 2022). No significant difference was found between COCP pre-treatment and no pre-treatment for cumulative live birth rate (38.7% (12/31) vs. 47.6% (10/21)), live birth rate (31.8% (7/22) vs. 46.7% (7/15)). There was also no significant difference in the number of MII oocytes between the study and control group (6.32±5.16 vs. 6.15±4.68).

An RCT, more recent than the meta-analysis, also investigated the effect of COCP pre-treatment compared to no pre-treatment in a GnRH antagonist protocol in women with PCOS (Gao et al., 2024).

The COCP consisted of ethinyl estradiol (0.03 mg) and drospirenone (3 mg) and were administered daily for 21 days to induce menstruation, followed by 7 days of washout. No significant differences were observed between COCP pre-treatment and no pre-treatment for cumulative live birth rate (ITT, 74.4% (90/121) vs. 77.7% (94/121)), live birth rate (per protocol, 52.8% (56/106) vs. 55.1% (60/109)) or incidence of moderate to severe OHSS (ITT: 6.6% (8/121) vs. 10.7% (13/121)).

Recommendations

COCP pre-treatment is not recommended in the GnRH antagonist protocol with FSH alone stimulation, because of reduced efficacy. [updated]	Strong	⊕⊕◯◯

A minimal wash out period of 5 days may be applied if COCP is used for programming cycle in the case of a fresh transfer. [2025]	GPP

Justification

There is low-quality evidence of a lower live birth/ongoing pregnancy rate using COCP pre-treatment in GnRH antagonist protocols compared with no pre-treatment. These results are conflicting with a more recent network meta-analysis that reported no significant difference in live birth rate when comparing COCP pre-treatment to no pre-treatment in GnRH antagonist protocol only (RR 0.93, 95% CI 0.56-1.54, 3 RCT, n=199) (Venetis et al., 2023). Due to methodological shortcomings, this network meta-analysis could not be included in the evidence section. There is low-quality evidence regarding OHSS incidence.

The type of COCP pre-treatment used in the studies was heterogenous regarding the oestrogen and progestogen components, as well as the starting days or duration of COCP. The duration varied from 12 to 28 days, and 3 consecutives cycles in one study. In some studies, the duration was fixed and variable in others, depending on the purpose of scheduling or not (Farquhar et al., 2017). Another important condition with heterogeneity between studies is the wash-out period between the stop of COCP pre-treatment and the start of stimulation. This may have on important impact on hormonal environment (Cedrin-Durnerin et al., 2007).

Lastly, it is important to note however that the available evidence comes predominantly from r-hFSH stimulation in GnRH-antagonist protocols and the usage of ethinyl oestradiol combined with either levonorgestrel or desogestrel as COCP. Whether a negative COCP effect exists in other treatment protocols or when using other COCPs is unknown.

GnRH antagonist pre-treatment

Evidence

In an RCT, GnRH antagonist pre-treatment in a GnRH antagonist protocol was investigated in 136 normal ovulatory women (Zhang et al., 2021). In the study group, ovarian stimulation was initiated after 3 days of GnRH antagonist pretreatment. No significant differences were found between GnRH

antagonist pre-treatment and no pre-treatment for live birth rate per embryo transfer (33.9% (20/59) vs. 43.1% (25/58)) or incidence of moderate to severe OHSS (1.5% (1/68) vs. 2.9% (2/68)). Furthermore, neither the ongoing pregnancy rate (33.9% (20/59) vs. 45.6% (26/58) or the number of MII oocytes (7 (6.0-11.0) vs. 9.0 (5.3-12.0) was different between the study and the control group.

One small RCT in 69 normogonadotropic women (not PCOS, not-poor responder) reported no difference in ongoing pregnancy rate (42% vs. 33%, 95% CI -13-3) and number of oocytes (12.8±7.8 vs. 9.9±4.9) comparing early follicular pre-treatment with GnRH antagonist (delayed start protocol) compared to no pre-treatment in fixed antagonist protocol (Blockeel et al., 2011).

In an RCT, including 110 women with PCOS (study group n=50, control group n=60), the effect of three days of GnRH antagonist pretreatment on the pregnancy outcomes in GnRH antagonist protocols for IVF/ICSI was evaluated (Eftekhar et al., 2018). The GnRH antagonist was administrated for 3 days, starting on day 2 before the start of a GnRH flexible antagonist protocol with r-hFSH 150 IU on cycle day 5. The incidence of moderate to severe risk of OHSS was not significantly different between GnRH antagonist pre-treatment and no pre-treatment (39% (15/38) vs. 36% (18/50). Furthermore, neither the ongoing pregnancy rate (28% (6/38) vs. 9% (2/50) or the number of MII oocytes (14.65±8.30 vs. 14.10±8.79) was different between the study and the control group.

Recommendation

GnRH antagonist pre-treatment before ovarian stimulation in a delayed-start gonadotrophin protocol is probably not recommended. [2019]	Conditional ⊕◯◯◯

Justification

There is very low-quality evidence that ongoing pregnancy rate per embryo transfer and number of oocytes are not statistically different with GnRH antagonist pre-treatment in young normogonadotropic women (Blockeel et al., 2011). Only one RCT reported on women with PCOS and reported no significant differences in efficacy and safety (Eftekhar et al., 2018).

hCG PRE-TREATMENT

Evidence

In an RCT, the effect of short term pre-gonadotropin administration of hCG (n=27) was assessed in women entering an ICSI cycle and compared to no pre-treatment (n=19) (Beretsos et al., 2009). The long luteal GnRH agonist protocol with r-hFSH and 7 days hCG 200 IU/day before r-hFSH fixed dose of 200 IU daily was used in the study group. Clinical pregnancy rate was significantly higher in the hCG pre-treatment group (46.2% vs. 31.8%).

Recommendation

hCG pre-treatment can only be used in the context of a clinical trial. [2025]	Research only

Justification

Even though published results show a benefit of hCG pre-treatment before ovarian stimulation, current evidence is a single, very small RCT. Insufficient data are available to support or refute the use of hCG pre-treatment.

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PART C: Pituitary suppression and ovarian stimulation

4. Ovarian stimulation protocols

PICO QUESTION: ACCORDING TO PREDICTED RESPONSE-BASED STRATIFICATION, WHICH STIMULATION PROTOCOL IS MOST EFFICIENT AND SAFE?

Ovarian stimulation for IVF/ICSI aims at obtaining several oocytes that will be turned into embryo's through the laboratory process of in vitro fertilisation. These embryos can then be placed in the uterine cavity within the window of implantation in order to achieve a pregnancy leading to live birth. The contribution of ovarian stimulation to the maximisation of success is under debate for many years. The key issues here are 'how many oocytes do we need to ensure at least one good quality embryo for transfer', 'do more oocytes imply a better chance of obtaining a pregnancy', 'how can we limit the risk of OHSS by the way we stimulate the ovaries' and 'how will the level of FSH exposure contribute to creating optimal live birth rates and safety'. In this chapter, the role of the individual predicted ovarian response and the various FSH dosing regimens will be discussed. The policy of getting only a few oocytes more than the one oocyte that will occur in a natural cycle is known under the term MILD stimulation. This is however, a non-standardised term. ICMART describes mild stimulation as a protocol in which the ovaries are stimulated with gonadotropins, and/or other pharmacological compounds, with the intention of limiting the number of oocytes following stimulation for IVF. The definition is often based on the number of follicles developed. It is seen as the intended approach. However, it is difficult to decide on a gonadotropin starting dose to obtain a set number of follicles. In literature, this results in high heterogeneity within study protocols. Therefore, data on this approach will therefore not be presented in this guideline.

A. HIGH RESPONDER

DELAYED-START STIMULATION

Evidence

In an RCT, delayed start of r-hFSH (day 4; n=22) was studied and compared to conventional start of r-hFSH (day 2; n=21) in expected high responders in a GnRH antagonist protocol (Revelli et al., 2020). Comparing delayed start stimulation to conventional start stimulation in expected high responders, both the cumulative live birth per oocyte pick-up (52.4% (11/21) vs. 57.1% (12/21)) and the clinical pregnancy rate per started cycle (50.0% (11/22) vs. 47.6% (10/21) were comparable.

In an RCT, delayed start stimulation with 150 IU r-hFSH from day 4 in a GnRH antagonist protocol (n=203) was compared to a conventional long GnRH agonist protocol with r-hFSH (150 IU; n=207) in women with an expected high response to ovarian stimulation (non-PCOS) (Casano et al., 2012). No

significant differences were reported between the delayed start and the conventional protocol for live birth rate per started cycle (24.9% (51/205) vs. 26.6% (55/207)) or OHSS rate (1.6% vs. 2.0%).

Recommendation

Delayed-start ovarian stimulation is probably not recommended routinely in predicted high responders to decrease the risk of OHSS. [2025]	Conditional ⊕◯◯◯

Justification

There is insufficient evidence to support or refute the use of delayed start ovarian stimulation for high responders, compared to conventional ovarian stimulation.

The rationale for delayed-start stimulation is to decrease the risk of OHSS, however, no benefit for safety in terms of OHSS has been observed in current studies. Other studies on random-start stimulation have not shown a disadvantage in efficacy in terms of live birth rate.

MODIFIED NATURAL CYCLE

Modified natural cycle (MNC) for IVF is defined as a procedure in which one or more oocytes are collected from the ovaries during a spontaneous menstrual cycle (Zegers-Hochschild et al., 2017). Pharmacological compounds are administered with the sole purpose of blocking the spontaneous LH surge and/or inducing final oocyte maturation (GLOSSARY).

There is no evidence to justify the use of NC or MNC for OS in high responders.

DOSE COMPARISONS

Evidence

A Cochrane meta-analysis[5] including 3 RCTs, including women with a high ovarian response to stimulation, investigated direct gonadotropin dose comparisons (Ngwenya et al., 2024). Since Arce et al. 2014 and Ishihara et al., 2021 were dose-response studies of a novel gonadotropin, the dosages were reported in µg and translation to IU was not possible, therefore, pooling of the results was also not possible.

The RCT by Ishihara *et al.*, compared ovarian stimulation with either 6 (n=25), 9 (n=25), 12 µg (n=25) r-hFSH in a GnRH antagonist protocol in women with a high ovarian response to stimulation (Ishihara et al., 2021). Live birth rates were not significantly different between dosages of r-hFSH (16% (4/25), 24% (6/25), 24% (6/25)). The rates of moderate or severe OHSS across the three dose groups were 16%, 8%, and 16%. The number of oocytes retrieved were 8±4.1 vs. 11±5.6 and 13±6.4.

The RCT by Oudshoorn *et al.*, including 521 predicted high responders, compared ovarian stimulation with 100 IU FSH (n=255) to ovarian stimulation with 150 IU FSH (n=266) either in a GnRH agonist or GnRH antagonist protocol (Oudshoorn et al., 2017). Comparable rates of ongoing pregnancy within 18 months of follow-up resulting in live birth were reported (66.3% vs. 69.5%; RR 0.953, 95% CI 0.85–1.07)

[5] The Cochrane review by Lensen *et al.* 2017 was replaced by the updated Cochrane review.

and 1st cycle live birth (fresh and cryopreserved embryos) (36.0% vs. 39.1%). Lower-dose stimulation resulted in significantly lower OHSS rate (5.2% vs. 11.8%) as compared with conventional ovarian stimulation (Oudshoorn et al., 2017).

The RCT by Arce *et al.*, compared ovarian stimulation with either 5.2 (=23), 6.9 (n=26), 8.6 (n=24), 10.3 (n=24), or 12.1 µg (n=26) of r-hFSH, or 11 µg (150 IU, n=25)) of follitropin alfa in a GnRH antagonist cycle in women with a high ovarian response to stimulation (AMH 15.0-44.9 pmol/L) (Arce et al., 2014). There was no significant difference between the different dosages and the conventional dose of follitropin alfa for cumulative live birth rate (43% (10/23), 54% (14/26), 46% (11/24), 38% (9/24), 50% (13/26) vs. 56% (14/25)) or live birth rate (39% (9/23), 42% (11/26), 38% (9/24), 25% (6/24), 46% (12/26) vs. 48% (12/25). A statistically significant dose–response relationship with respect to number of oocytes retrieved was established for r-hFSH (5.9±3.9, 9.1±6.4, 10.6±4.8, 13.6±7.8, 14.4±5.8 vs. 12.4±5.4). Two cases of early OHSS were reported in the highest r-hFSH dose groups (10.3 and 12.1 µg, respectively), and three late OHSS (one in the 8.6 µg group and two in the 12.1 µg group).

Recommendation

A reduced gonadotropin dose (100 to <150 IU) is probably recommended to decrease the risk of OHSS in predicted high responders. [2025]	Conditional	⊕◯◯◯

The GnRH antagonist protocol is recommended for predicted high responders. [updated]	Strong	⊕◯◯◯

Justification

Conventional dosing is 150-225 IU. In predicted high responders, a reduced gonadotropin dose (100 to <150 IU) is probably recommended, based on other patient characteristics, the choice of final oocyte maturation trigger and embryo transfer strategy.

The recommendation is extrapolated from a stratified group analysis of three RCTs in women with high levels of AMH. Two RCTs were dose-finding studies for a new follitropin in the GnRH antagonist protocol (Arce et al., 2014, Ishihara et al., 2021) and in the third RCT, the majority of the patients were treated with the long GnRH agonist protocol. The data from the Oudshoorn trial shows that lowering gonadotropin dosage may increase safety in GnRH agonist protocol. However, the mix of GnRH agonist and antagonist protocols, the per protocol allowance of dose adjustments in 2nd cycle and the very high cycle cancellation rate in high responders should be carefully considered when interpreting the available evidence. Furthermore, the fact that a freeze-all policy was not adopted in the trial, a strategy which may reflects current clinical practice, questions the potential negative effects of conventional dosage stimulation in terms of cumulative pregnancy rate and OHSS rates. The two dose-finding trials were not powered to show a difference in OHSS incidence.

B. NORMAL RESPONDER

DELAYED-START STIMULATION

Evidence

In an RCT, delayed start of r-hFSH (day 4; n=19) was studied and compared to conventional start of r-hFSH (day 2; n=20) in expected normal responders (Revelli et al., 2020). Comparing delayed start stimulation to conventional start stimulation in expected normal responders, both the cumulative live birth per oocyte pick-up (16.7% (3/18) vs. 26.3% (5/19)) and the clinical pregnancy rate per started cycle (16.7% (3/18) vs. 26.3% (5/19)) were comparable.

In an RCT, women with an expected normal response to ovarian stimulation, starting their first IVF cycle and younger than 35 years were randomised to receive either ovarian stimulation with hMG (150 IU daily) without pituitary suppression (n=30) or a long GnRH agonist protocol with r-hFSH (150-300 IU; n=30) (Lou and Huang, 2010). No significant difference was reported when comparing the study group to the control group for mild OHSS (0 vs. 6.7% (2/30)), ongoing pregnancy rate per started cycle (26.7% (8/30) vs. 23.3% (7/30)) or clinical pregnancy rate per started cycle (30.0% (9/30) vs. 30.0% (9/30)).

Three older RCTs compared the late-start FSH (fixed dose of 150 IU starting on cycle day 5) with conventional-start FSH (Baart et al., 2007, Blockeel et al., 2011, Hohmann et al., 2003). The RCT by Baart *et al.* compared late-start FSH in the GnRH antagonist protocol with conventional FSH stimulation in the long GnRH agonist protocol in 111 women and reported no significant difference in ongoing pregnancy rate (19% (12/63) vs. 17% (7/41)). However, significantly less oocytes were retrieved with the late-start FSH protocol (8.3±4.7 vs. 12.1±5.7) (Baart, et al., 2007). The RCT by Hohmann *et al.* including 104 predicted normal responders, compared late-start with conventional-start FSH in the GnRH antagonist protocol and reported no difference in ongoing pregnancy rate (16% (8/49) vs. 17% (8/48) or number of oocytes retrieved (7 (1-27) vs. 8 (2-31)) (Hohmann et al., 2003). The RCT by Blockeel *et al.* including 76 predicted normal responders also compared late-start with conventional-start FSH in the GnRH antagonist protocol and also reported no significant difference in ongoing pregnancy rate (25% 10/40 vs. 28% (10/36) (Blockeel et al., 2011).

Recommendation

Delayed-start ovarian stimulation is probably not recommended over a conventional gonadotrophin dose for predicted normal responders. [2025]	Conditional ⊕◯◯◯

Justification

The rationale to delay the start of ovarian stimulation would be the prevention of OHSS. However, this topic has not been researched well and current RCTs were not powered to show a difference in OHSS rate. As a result, no benefit for safety in terms of OHSS has been observed in current studies.

There is insufficient evidence to support or refute the use of delayed start ovarian stimulation for normal responders, compared to conventional ovarian stimulation.

DOSE COMPARISONS

Evidence

A Cochrane meta-analysis[6] including 12 RCTs, including women with a normal ovarian response to stimulation, investigated direct gonadotropin dose comparisons (Ngwenya et al., 2024). For moderate or severe OHSS, the estimates of difference between the dose comparisons were very imprecise, there is little information about the true treatment effect.

200 IU vs. 100 UI

No significant difference in live birth/ongoing pregnancy rate was observed of the different doses (OR 0.88, 95% CI 0.57-1.36, 2 RCTs, 522 women) (Ngwenya et al., 2024). No significant difference in the incidence of severe OHSS was found with the different gonadotropin doses (peto OR 0.14, 95% CI 0.00-6.96, 2 RCT, 522 women) or in the incidence of moderate to severe OHSS (peto OR 0.62, 95% CI 0.21-1.87, 2 RCTs, 522 women). The pooled estimate suggests a higher number of oocytes were obtained with the higher dose of gonadotropin (ratio of mean oocytes 1.58, 95% CI 1.43-1.77, 2 RCTs, 330 women). However, the statistical heterogeneity was high.

225/200 IU vs. 150 UI

No significant difference in live birth rate was observed of the different doses (OR 0.98, 95% CI 0.70-1.36, 2 RCTs, 211 women) (Ngwenya et al., 2024). Two RCTs reported on cumulative live birth rate, using two different definitions. However, these data could neither confirm nor rule out dose effects on cumulative live birth. No significant difference in the incidence of severe OHSS was found with the different gonadotropin doses (peto OR 1.00, 95% CI 0.20-5.02, 4 RCT, 740 women) or in the incidence of moderate to severe OHSS (peto OR 1.21, 95% CI 0.51-2.85, 4 RCTs, 740 women). The pooled estimate suggests a higher number of oocytes were obtained with the higher dose of gonadotropin (ratio of mean oocytes 1.16, 95% CI 1.08-1.25, 6 RCTs, 872 women).

300 IU vs. 150 UI

No clear impact of different doses on the probability of live birth were found (OR 0.80, 95% 0.19-3.42, 1 RCT, 37 women) (Ngwenya et al., 2024, Shyamsunder et al., 2021). The ratio of mean oocytes was 1.23 (95% CI 0.89-1.72, 57 women).

300 IU vs. 225 UI

No clear impact of different doses on the probability of live birth were found (OR 0.65, 95% 0.32-1.32, 1 RCT, 47 women (Jayaprakasan et al., 2010, Ngwenya et al., 2024). No significant difference in the incidence of severe OHSS was found with the different gonadotropin doses (peto OR 0.14, 95% CI 0.00-6.92, 1 RCT, 135 women) or in the incidence of moderate to severe OHSS (peto OR 0.67, 95% CI 0.11-3.99, 1 RCT, 135 women). The available evidence could not rule out or confirm an effect of gonadotropin dosing on the number of retrieved oocytes (ratio of mean oocytes 1.03, 95% CI 0.84-1.26, 1 RCT, 135 women).

[6] The Cochrane review by Lensen *et al.* 2017 on dose comparison and the meta-analysis on mild gonadotropin dosing by Sterrenburg *et al.*, 2011 were replaced by the updated Cochrane review.

Recommendation

Neither a reduced nor increased gonadotrophin dose is probably recommended over a conventional gonadotrophin dose (equivalent to 150-225 IU) for predicted normal responders. [updated]	Conditional ⊕◯◯◯

Justification

In the published meta-analysis, the chance of live birth in normal responders is not affected by modifications in the FSH starting dose. The heterogeneity of the studies is too high to be conclusive on the impact of dose and type of FSH on the number of retrieved oocytes as well as on the risk of OHSS.

The meta-analysis suggests that the optimal daily r-hFSH stimulation dose is 150 IU/day in predicted normal responders. Although available studies suggest similar efficacy in terms of clinical pregnancy rate between reduced-dose and conventional-dose stimulation, the lower number of oocytes retrieved could potentially compromise cumulative live birth rate in predicted normal responders.

The recommendation is based on studies conducted in GnRH agonist protocols, however, the guideline group thinks that the recommendation may also apply to GnRH antagonist protocol due to the increased safety with the option of the GnRH agonist trigger.

C. LOW RESPONDER

DELAYED-START STIMULATION

Evidence

In an RCT, delayed start of r-hFSH (day 4; n=15) was studied and compared to conventional start of r-hFSH (day 2; n=16) in expected poor responders (Revelli et al., 2020). Comparing delayed start stimulation to conventional start stimulation in expected poor responders, both the cumulative live birth per oocyte pick-up (0% (0/9) vs. 23.1% (3/13)) and the clinical pregnancy rate per started cycle (0% (0/15) vs. 18.7% (3/16)) were significantly lower.

Recommendation

Delayed start ovarian stimulation is probably not recommended for predicted low responders. [2025]	Conditional ⊕◯◯◯

Justification

There is insufficient evidence to support or refute the use of delayed start ovarian stimulation for low responders, compared to conventional ovarian stimulation.

MODIFIED NATURAL CYCLE

Evidence

In an RCT, 90 women with a low response to ovarian stimulation were randomised to receive either minimal ovarian stimulation (150 IU from day 7/8) or conventional stimulation (225 IU) in a GnRH antagonist protocol (Kim et al., 2009). No significant difference in clinical pregnancy per cycle was reported (13.3% (6/45) vs. 17.8% (8/45)). The number of MII oocytes retrieved was significantly lower in the lower dose gondadotropins group (1.3±0.8 vs. 2.5±1.4).

One RCT compared MNC-IVF with a microdose GnRH agonist flare protocol in 125 poor responder women (215 cycles) and reported no significant difference in pregnancy rate (6.1% vs. 6.9%) (Morgia et al., 2004).

In a retrospective cohort study, natural cycle IVF (n=230) was compared to conventional ovarian stimulation in GnRH antagonist protocol (n=355) in poor ovarian responders and aged ≥40 years (De Marco et al., 2021). In the natural cycle IVF group, no treatment was administered for the selection and recruitment of follicles, however, ovulation was triggered with 10.000 IU of hCG. Comparing natural cycle IVF to conventional stimulation, no significant difference was seen in cumulative live birth rate (9.6% (22/230) vs. 14.4% (51/355)), however, the cumulative pregnancy rate per cycle was significantly higher with conventional stimulation (6.3% (36/576) vs. 12.9% (70/543)).

Recommendation

The use of modified natural cycle is probably not routinely recommended over conventional stimulation for low responders. [updated]	Conditional ⊕◯◯◯

The GDG recognises that low responders are a heterogeneous group and in women with very low ovarian reserve, clinicians could choose to use a modified natural cycle. [2025]	GPP

Justification

There are no good-quality, controlled studies available to support the use of modified natural cycle or natural cycle IVF in low responders. Furthermore, the number of oocytes were lower with modified natural cycle compared to conventional stimulation. Although there are no good quality studies looking at modified natural cycle in women with very low number of follicles, who would not benefit significantly from conventional stimulation, a modified natural cycle could be considered.

DOSE COMPARISONS

Evidence

A Cochrane meta-analysis[7] including 6 RCTs, including women with a poor ovarian response to stimulation, investigated direct gonadotropin dose comparisons (Ngwenya et al., 2024). For live birth or ongoing pregnancy, the estimates of difference between the dose comparisons were very imprecise, there is little information about the true treatment effect.

300/450 IU vs. 150 IU

The Cochrane meta-analysis reported no significant difference in live birth/ongoing pregnancy rates (3 RCT, OR 1.20, 95% CI 0.78-1.86, 538 women) between the 150 IU and 300/450 IU dose of gonadotropins and no cases of moderate or severe OHSS were observed in either group. However, the pooled effect suggests that slightly more oocytes were retrieved in the higher gonadotropin dose group (, ratio of mean oocytes 1.97, 95% CI 1.70 to 2.29, 3 RCT, 947 women) (Ngwenya et al., 2024).

400/450 IU vs. 300 IU

The Cochrane meta-analysis reported no significant difference in ongoing pregnancy rate (OR 0.77, 95% CI 0.19-3.19, 1 RCT, 62 women) or number of oocytes retrieved (ratio of mean oocytes 0.97, 95% CI 0.74 to 1.27, 2 RCT, 110 women) between the 300 IU and 400/450 IU dose of gonadotropins and no cases of moderate or severe OHSS in either group (Ngwenya et al., 2024).

600 IU vs. 450 UI

The Cochrane meta-analysis reported no significant difference in live birth rate (OR 1.33, 95% CI 0.71-2.52, 1 RCT, 356 women), or number of oocytes retrieved (ratio of mean oocytes 1.08, 95% CI 0.96 to 1.22, 1 RCT, 356 women) between the 450 IU and 600 IU dose of gonadotropins and one case of moderate OHSS in the 600 IU dose group (Lefebvre et al., 2015, Ngwenya et al., 2024).

Recommendation

A gonadotropin dose higher than 300 IU is not recommended for predicted low responders. [2019]	Strong	⊕◯◯◯

Justification

Conventional gonadotropin dosing (equivalent to 150-225 IU per day) suits most of the predicted low responder patients. There is evidence that a higher gonadotropin dose than 150 IU results in a slightly higher number of oocytes in low responders, and more chances of having an embryo for transfer. However, there is no evidence of any benefit of higher FSH dosing for live birth/ongoing pregnancy rates. Still, the sample sizes of the studies are small and therefore not sufficient to provide evidence on the benefits of various dosing levels over the standard dose for the outcome live birth.

There is also unlikely to be a significant benefit with doses >300 IU daily, as comparisons with doses >300 IU did not show significant differences in the above mentioned outcomes.

[7] The Cochrane review by Lensen *et al.* 2017 was replaced by the updated Cochrane review.

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5. Pituitary suppression regimens

PICO Question: Which pituitary suppression protocol is preferable?

GnRH agonist protocols

Evidence

A Cochrane meta-analysis including 40 RCTs compared different GnRH agonist protocols (Siristatidis et al., 2025).

Long vs short GnRH agonist protocol[8]

The Cochrane meta-analysis found no significant difference in live birth rate/ongoing pregnancy rate per woman randomised (OR 1.45, 95% CI 0.83-2.52, 5 RCT, 381 women) between the long and the short GnRH agonist protocol (Siristatidis et al., 2025). None of the included studies for this comparison reported OHSS rates.

An RCT, not included in the Cochrane meta-analysis, including 131 women also reported no significant difference in clinical pregnancy rate between the long and the short GnRH agonist protocol (19.6% vs. 8.3%) (Ravhon et al., 2000).

However, another RCT, not included in the Cochrane meta-analysis, including 220 women ≥40 years of age, reported a significantly reduced clinical pregnancy rate with the short GnRH agonist protocol as compared to the long (10.9% (12/110) vs. 22.7% (25/110)) (Sbracia et al., 2005).

Long vs ultrashort GnRH agonist protocol

The Cochrane meta-analysis found no significant difference in live birth rate when a long protocol was compared with an ultrashort GnRH agonist protocol (1 RCT, OR 1.78, 95% CI 0.72-4.36, 150 women) (Kingsland et al., 1992, Siristatidis et al., 2025). There were no data on adverse outcomes reported.

Short vs ultrashort GnRH agonist protocol

The Cochrane meta-analysis reported no significant difference in the clinical pregnancy rate when a short protocol was compared with an ultrashort protocol (1 RCT, OR 1.33, 95% CI 0.47-3.81, 82 women) (Berker et al., 2010, Siristatidis et al., 2025). There were no data on adverse outcomes reported.

Long GnRH agonist protocol: luteal vs follicular start

The Cochrane meta-analysis found no significant difference in live birth/ongoing pregnancy rates when GnRH agonist was commenced in the luteal or follicular phase for the long protocol (1 RCT, OR 1.89, 95% CI 0.87-4.10, 223 women) (Siristatidis et al., 2025, Urbancsek and Witthaus, 1996). There were no data on adverse outcomes reported.

The RCT by Ravhon *et al.*, including 125 women, also reported no significant difference in pregnancy rate when GnRH agonist was started on day 2 versus day 21 (19.6% vs. 18.6%) (Ravhon et al., 2000).

[8] A meta-analysis was cited here in the previous version of the guideline on the long versus short GnRH agonist protocol in women with adenomyosis. The reader is referred to the Good Practice Recommendations paper on Adenomyosis for updated advice on fertility treatment in women with adenomyosis.

Long GnRH agonist protocol: continuation vs stopping GnRH agonist at start of stimulation

The Cochrane meta-analysis found no significant difference in the number of ongoing pregnancies (OR 0.66, 95% CI 0.30-1.49, 2 RCT, 194 women), clinical pregnancy rate (OR 0.76, 95% CI 0.40-1.44, 3 RCT, 264 women) when GnRH agonist was stopped compared with when it was continued (Siristatidis et al., 2025).

Long agonist protocol: continuation of same-dose vs reduced-dose GnRH agonist until trigger

The Cochrane meta-analysis found no significant difference in live birth/ongoing pregnancy rate (OR 1.59, 95% CI 0.66-3.87, 1 RCT, 96 women) or clinical pregnancy rate when the dose of GnRH agonist was reduced compared with when the same dose was continued (4 RCT, OR 1.02, 95% CI 0.68-1.52, 407 women) (Siristatidis et al., 2025). There was no significant difference in OHSS rate between continuing or reducing the GnRH agonist dose (OR 0.47, 95% CI 0.04-5.35, 1 RCT, 96 women).

Recommendation

If GnRH agonists are used, the long GnRH agonist protocol is recommended over the short or ultrashort GnRH agonist protocol. [updated]	Strong	⊕⊕◯◯

Justification

The long GnRH agonist protocol has proven to be highly efficient for preventing LH surge. Since its introduction, there has been a reduction of cycle cancellation, increased number of oocytes retrieved and higher pregnancy rates. Compared to other GnRH agonist protocols, the long protocol provides better efficacy and is supported by a larger body of evidence.

The short GnRH agonist protocol appeared as a modification of the classic long protocol with the aim of improving cycle outcome in low responders and older patients. The current evidence available shows that this goal is not achieved.

GnRH antagonist protocols

Evidence

A systematic review and meta-analysis[9] including 36 RCTs in the general IVF population, compared the GnRH antagonist protocol with the long GnRH agonist protocol. They did not include RCTs reporting on early follicle phase start-up GnRH antagonist or long-acting follicular GnRH agonist protocols (Liu et al., 2023). No significant difference was found between the GnRH antagonist and long GnRH agonist protocol for live birth rate (RR 0.95, 95% CI 0.86-1.06, 10 RCT, 2939 women) or ongoing pregnancy rate (RR 0.94, 95% CI 0.86-1.03). However, the risk of OHSS was significantly lower with the GnRH antagonist protocol (RR 0.84, 95% CI 0.75-0.94, 17 RCT, 4892 women), especially the risk of moderate or severe OHSS (RR 0.56, 95% CI 0.40-0.79, 15 RCT, 4481 women).

[9] The Cochrane review by Al-Inany *et al.*, 2016 was replaced by a newer meta-analysis. The RCTs by Friedler *et al.*, 2006 and Toftager *et al.*, 2016 are included in the meta-analysis and therefore no longer mentioned separately.

An RCT, not included in the meta-analysis, including 132 women, reported a significantly higher clinical pregnancy rate with the long GnRH agonist protocol as compared to the GnRH antagonist protocol (49.2% vs. 26.2%). One case of mild OHSS developed in each group (Verpoest et al., 2017).

Two RCTs including respectively 160 cycles and 96 women, compared the GnRH antagonist protocol with the short GnRH agonist protocol (Gordts et al., 2012, Maldonado et al., 2013). Gordts *et al*. reported an ongoing pregnancy rate of 21% and a live birth rate of 19% in GnRH antagonist cycles compared to 20% and 20% respectively in GnRH agonist cycles, which are both not statistically different (Gordts et al., 2012). However, Maldonado *et al*. reported a significantly lower clinical pregnancy rate (31.0% (13/48) vs. 52.1% (25/48)) in the short GnRH agonist protocol as compared to the GnRH antagonist protocol (Maldonado et al., 2013).

A systematic review and meta-analysis, including 6 RCTs and 907 participants, compared fixed and flexible GnRH antagonist protocols (Venetis et al., 2023). A significantly lower ongoing pregnancy rate was reported with flexible versus fixed GnRH antagonist protocols (RR 0.76, 95% CI 0.62-0.94.

Recommendation

The GnRH antagonist protocol is recommended over the GnRH agonist protocols given the comparable efficacy and higher safety in the general IVF/ICSI population. [2019]	Strong	⊕⊕⊕◯

The fixed GnRH antagonist protocol is probably recommended over the flexible GnRH antagonist protocol. [2025]	Conditional	⊕⊕◯◯

Justification

The introduction of GnRH antagonist allowed overcoming the significant undesirable effects of the GnRH agonist protocols. Although the first studies reported slight but consistent lower pregnancy rates, which delayed the implementation of the GnRH antagonist protocol, several large meta-analyses published in the past 10 years support similar live birth rates. There is far less evidence for the short GnRH agonist protocol, however, results are expected to be similar as for the long GnRH agonist protocol.

Although there is high heterogeneity in RCTs comparing flexible to fixed GnRH antagonist protocols, results show that ongoing pregnancy rates are lower with a flexible GnRH antagonist protocol (Venetis et al., 2023).

PROGESTIN PROTOCOLS

The use of oral progestins to prevent the LH surge is a novel protocol in which GnRH analogues are not used. Progestin administration along the whole stimulation will keep the pituitary suppressed and has shown to prevent untimely LH surges effectively. However, the use of this protocol implies the freezing

of all the embryos and transfer in a subsequent frozen embryo replacement cycle, as the endometrium would not be receptive in a fresh cycle due to the effect of the progestins.

Evidence

Progestogens vs. GnRH analogues

A Cochrane systematic review and meta-analysis including 100 normal responders from 1 RCT, compared ovarian stimulation with gonadotropins in combination with progestogens with gonadotropins combined with GnRH antagonist (Ghasemzadeh et al., 2019, Glujovsky et al., 2023). Significantly more MII oocytes were retrieved after stimulation with progestogens (10.8±5.8 vs. 7±4.2; MD 3.80, 95% CI 1.82 to 5.78). A more recent RCT, including 200 unselected women undergoing IVF/ICSI, compared dydrogesterone with the flexible GnRH antagonist protocol for pituitary suppression (Hossein Rashidi et al., 2020). No significant difference was reported in clinical pregnancy rate per first embryo transfer (43.95% (40/97) vs. 49.50% (45/95)) between dydrogesterone and GnRH antagonist for pituitary suppression, however, significantly more MII oocytes were retrieved after dydrogesterone treatment (7.90±3.62 vs. 6.26±3.64).

In an RCT, 348 women with normal ovarian reserve were randomised to receive ovarian stimulation in a progestin protocol with freeze-all (n=174) or GnRH antagonist protocol with fresh transfer first (n=174) (Ye et al., 2024). No significant difference was reported between the progestin protocol group and the GnRH antagonist group for cumulative live birth rate per woman (55.7% (97/174) vs. 52.9% (92/174)) or clinical pregnancy rate per transfer (57% (114/200 vs. 55.9% (109/195)). No cases of OHSS were reported in either group.

The Cochrane systematic review and meta-analysis including 260 women from 1 RCT, compared ovarian stimulation with gonadotropins in combination with progestogens with gonadotropins combined with GnRH agonist (Glujovsky et al., 2023, Xi et al., 2020). No significant difference was found for live birth/ongoing pregnancy rate (45.3% (59/130) vs. 46.9% (61/130); OR 0.94, 95% 0.58-1.53), OHSS rate (0% (0/130) vs. 2.3% (3/130); OR 0.14, 95% CI 0.01-2.73), clinical pregnancy rate (50% (65/130) vs. 53.1% (69/130); OR 0.88, 95% CI 0.54-1.44) or number of MII oocytes (10.3±5.8 vs. 10.1±5.2; MD 0.20, 95% CI -1.14 to 1.54).

The Cochrane systematic review and meta-analysis including 340 poor responders from 1 RCT, compared ovarian stimulation with gonadotropins in combination with progestogens with gonadotropins combined with GnRH antagonist (Chen et al., 2019, Glujovsky et al., 2023). No significant difference was found for live birth rate/ongoing pregnancy rate (21.8% (37/170) vs. 18.2% (31/170); OR 1.25; 95% CI 0.73-2.13), clinical pregnancy rate (28.2% (48/170) vs. 22.9% (39/170); OR 1.32; 95% CI 0.81-2.16), or number of MII oocytes (3.2±2.4 vs. 2.8±2.2; MD 0.40; 95% CI -0.09 to 0.89).

In an RCT, 484 predicted suboptimal responders were randomly assigned to receive ovarian stimulation in a progestin protocol (n=236) compared to a GnRH antagonist protocol (n=248) with freeze-all in both groups (Cai et al., 2024). Cumulative live birth rate over 12 months was 44.4% (96/216) in the progestin protocol group compared to 48.9% (114/233) in the GnRH antagonist group (RR0.91, 95% 0.74-1.11). Live birth rate after the first transfer was 32.9% (71/216) with the progestin protocol compared to 34.3% (80/240) with the GnRH antagonist protocol (RR 0.96, 95% CI 0.74-1.24).

In a systematic review and meta-analysis 3 RCTs were included with women with PCOS, one comparing progestogens to the GnRH agonist short protocol and two comparing to the GnRH antagonist protocol

(Yang et al., 2023). No significant difference for live birth rate (OR 1.46, 95% CI 0.79-2.71, 167 cycles), OHSS rate (OR 0.19, 95% CI 0.01-4.11, 2 RCTs, 240 patients). Also, the number of MII oocytes retrieved was similar in both groups (MD -0.85; 95% CI -3.40 to 1.71, 3 RCTs, 358 patients).

In an RCT, 784 women with an anticipated high response to ovarian stimulation were randomised to follow a progestin protocol (n=392) or GnRH antagonist protocol (n=392) for IVF/ICSI with freeze-all in both groups (Chen et al., 2024). No significant difference was observed in cumulative live birth rate (54.6% (214/392) vs. 48.5% (190/392); ITT) or live birth rate after the first transfer (37.5% (147/392 vs. 32.7% (128/392); ITT).

Progestogens vs. other progestogens

Cochrane systematic review and meta-analysis[10] 4 mg vs. 10 mg MPA. No significant difference in live birth/ongoing pregnancy rate (53/150 vs. 39/150; OR 1.56; 95 CI 0.95-2.55), clinical pregnancy rate (73/150 vs. 87/150; OR 0.69; 95% CI 0.44-1.08) (Dong et al., 2017, Glujovsky et al., 2023). No cases of moderate or severe OHSS were reported.

One RCT including 516 women compared dydrogesterone with MPA for pituitary suppression and reported no significant difference in clinical pregnancy rate (57.6 (125/217) vs. 62.3% (132/212); OR 0.82, 95% CI 0.56-1.21) or number of oocytes retrieved (10.8±6.3 vs. 11.1±5.8) (Yu et al., 2018). No cases of moderate or severe OHSS were reported.

Recommendation

If freeze-all is planned, the use of progestin for pituitary suppression is probably equally recommended to GnRH analogues. [updated]	Conditional	⊕◯◯◯

Justification

Oral progestins are efficient in terms of pituitary suppression, with comparable oocyte yield and pregnancy outcomes as the GnRH short agonist protocol. This approach is easy, cheap and patient friendly.

Many of the studies use the term PPOS. The GDG would like to clarify that the terminology PPOS, i.e. progestin-primed ovarian stimulation is not correct. More correct terminology would be progestin protocol for pituitary suppression.

The progestin protocol approach is only feasible for OS cycles in which a fresh embryo transfer is not scheduled, such as fertility preservation, oocyte donors, PGT, or pre-planned freeze-all cycles.

Current evidence shows that euploidy rates and clinical outcomes in PGT are also similar between progestin and GnRH antagonist protocol (Qin et al., 2025, Wan et al., 2024, Zhou et al., 2025).

A meta-analysis including four retrospective cohort studies found no increased risk of congenital malformations with the use of progestins for pituitary suppression compared to GnRH agonist protocol (OR 0.92, 95% CI 0.63-1.34) (Zolfaroli et al., 2020). The results of sensitivity analysis by progestin type

[10] The cohort studies by Chen *et al.*, 2017, Hamdi *et al.*, 2018 and Kuang *et al.*, 2015 were excluded in the presence of several RCTs.

were consistent with the main results. These results are also in line with a more recent, very large retrospective cohort study, including 15382 PPOS cycles and 1352 GnRH antagonist cycles (Li et al., 2022). Congenital malformations were observed in 323 of 15,245 (2.1%) in the PPOS group and 27 of 1,248 (2.2%), with a nonsignificant difference.

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6. Types of gonadotropins and other ovarian stimulation drugs

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

A. GONADOTROPINS

Recombinant human FSH (r-hFSH)

Recombinant human FSH (r-hFSH) vs human menopausal gonadotropin (hMG)

Evidence

In a systematic review[11] and meta-analysis, ovarian stimulation with r-hFSH was compared to highly purified (hp)-hMG (Bordewijk et al., 2019). No significant difference was found for cumulative live birth rate when comparing ovarian stimulation with r-hFSH and hp-hMG (RR 0.91, 95% CI 0.80-1.04, 3 RCT, 2109 women). Live birth rate (RR 0.88, 95% CI 0.78-0.99, 7 RCT, 3397 women) and clinical pregnancy rate (RR 0.90, 95% CI 0.81-1.00, 7 RCT, 3397 women) were lower with r-hFSH for ovarian stimulation compared to hp-hMG.

An RCT, not included in the meta-analysis, included 160 women and also compared hMG to r-hFSH in the GnRH agonist protocol. No significant differences were reported for live birth rate (27.5% (11/40) vs. 40% (16/40)) between hMG and r-hFSH for OS (Parsanezhad et al., 2017).

An RCT compared the efficacy and safety of highly purified hMG (150 IU) and r-hFSH (150 IU) for ovarian stimulation with the GnRH antagonist protocol in a population of patients predicted to be high responders (Witz et al., 2020). Cumulative live birth rates per cycle start were 50.6% and 51.5% in hMG treated and r-hFSH-treated patients (difference: -0.8%, 95% CI -8.7% to 7.1%). Similarly, comparing hMG and r-hFSH, there was no significant difference in live birth rate after fresh (52.2% vs. 48.7%; difference 3.6, 95% CI –6.4 to 13.4) or frozen (63.4% vs. 50.8%; difference 12.7, 95% CI –0.9 to 26.2) embryo transfer. The incidence of OHSS was significantly lower with hMG compared to r-hFSH (9.7% (30/310) vs. 21.4% (66/309); difference -11.7%, 95% CI -17.3% to -6.1%).

A small RCT including 80 PCOS patients reported no significant difference in live birth rate (23.1% vs. 35.7%) or mild OHSS rate (0.0% (0/38) vs. 11.9% (5/42)) between hMG and r-hFSH for OS (Figen Turkcapar et al., 2013).

Recommendation

The use of recombinant human FSH (r-hFSH) and human menopausal gonadotropin (hMG) for ovarian stimulation is equally recommended. [2019]	Strong	⊕⊕⊕◯

[11] The Cochrane systematic review (van Wely *et al.*, 2011) that was mentioned here in the 2019 version of the guideline was replaced by a more recent meta-analysis. The RCTs by Devroey *et al.*, 2012 and Ye *et al.*, 2012 are included in the meta-analysis and therefore no longer mentioned separately.

Justification

The results from the meta-analysis suggest no significant difference in cumulative live birth rate and a slightly higher efficacy (LBR/PR) with hMG compared to r-hFSH in GnRH agonist cycles. Effects on OHSS rates were not reported in the meta-analysis.

For GnRH antagonist cycles, the evidence is less extensive, however the RCTs by Bosch *et al.* and Devroey *et al.* showed highly purified hMG to be at least as effective as r-hFSH in antagonist cycles (Bosch et al., 2008, Devroey et al., 2012). Similar results were reported by Witz *et al.* in high responders (Witz et al., 2020).

Studies for this question in PCOS and women of advanced age were limited, so that a potential difference between compounds in these subgroups cannot be ruled out based on the current evidence.

RECOMBINANT HUMAN FSH (R-HFSH) VS PURIFIED URINARY FSH (P-FSH)

Evidence

In a Cochrane systematic review and meta-analysis, use of r-hFSH was not associated with a higher probability of live birth as compared to p-FSH when downregulation was achieved with GnRH agonists (5 RCT, OR 1.26, 0.96-1.64, 1430 women). The meta-analysis reported no significant difference in OHSS rate between r-hFSH and p-FSH (6 RCT, OR 1.79, 95% CI 0.89 to 3.62, 1490 women) (van Wely et al., 2011).

Recommendation

The use of recombinant human FSH (r-hFSH) and purified FSH (p-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended. [2019]	Strong	⊕⊕◯◯

Justification

In patients undergoing ovarian stimulation for IVF/ICSI, the use of p-FSH is not preferable to r-hFSH when downregulation is achieved with GnRH agonists, according to the Cochrane meta-analysis. Studies comparing the use of the two FSH preparations (p-FSH and r-hFSH) in GnRH antagonist cycles are not present to allow evaluation of this statement in such a setting.

RECOMBINANT HUMAN FSH (R-HFSH) VS HIGHLY PURIFIED URINARY FSH (HP-FSH)

Evidence

In a systematic review and meta-analysis[12], ovarian stimulation with r-hFSH was compared to hp-FSH (Bordewijk et al., 2019). No significant difference was found between r-hFSH and hp-FSH for ovarian stimulation for live birth rate (RR 1.03, 95% CI 0.90-1.18, 12 RCTs, 2458 women) or clinical pregnancy rate (RR 1.03, 95% CI 0.94-1.13, 21 RCTs, 4165 women).

[12] The Cochrane systematic review (van Wely *et al.*, 2011) that was mentioned here in the 2019 version of the guideline was replaced by a more recent meta-analysis.

These observations are in line with the findings of several other RCTs not included in the systematic review in GnRH agonist cycles (Gholami et al., 2010, Murber et al., 2011, Parsanezhad et al., 2017, Selman et al., 2010, Selman et al., 2013). Three RCTs including respectively 70, 127 and 160 women reported no significant difference in live birth rate between r-hFSH and hp-FSH (respectively 31.3% vs. 31.4%; 16.1% vs. 18.4% and 40% vs. 22.5%) (Murber et al., 2011, Parsanezhad et al., 2017, Selman et al., 2013). Two RCTs reported no difference in clinical pregnancy rate between r-hFSH and hp-FSH (respectively 39.6% vs. 38.7% and 33.3% (21/65) vs. 39% (23/60)) (Gholami et al., 2010, Selman et al., 2010).

Two RCTs including respectively 84 and 160 women investigated the comparison of r-hFSH compared to hp-FSH in PCOS patients. There was no difference in clinical pregnancy rate (50% (21/42) vs. 50.2% (22/42) and 41.2% (33/80) vs. 45% (36/80)) or number of oocytes retrieved (13.83±7.07 vs. 17.1±8.66 and 13.03±5.56 vs. 14.17±4.89) between both groups (Aboulghar et al., 2010, Sohrabvand et al., 2012). Sohrabvand et al. also reported no difference in live birth rate (21.3% (17/80) vs. 23.8% (19/80)), slight OHSS (5% (4/80) vs. 6.3% (5/80)) or moderate to severe OHSS (2.5% (2/80) vs. 2.5% (2/80)) between groups (Sohrabvand et al., 2012).

Recommendation

The use of recombinant human FSH (r-hFSH) and highly purified FSH (hp-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended. [2019]	Strong	⊕⊕◯◯

Justification

In patients undergoing ovarian stimulation, the use of hp-FSH is not preferable to r-hFSH, when downregulation is achieved by GnRH agonists according to a Cochrane meta-analysis and confirmed in subsequently published studies. Studies comparing the use of the two FSH preparations (hp-FSH and r-hFSH) in GnRH antagonist cycles are not present to allow evaluation of this statement in such a setting.

Studies for this question in PCOS patients were limited, so that a potential difference between compounds in this subgroup cannot be ruled out based on the current evidence.

Recombinant (r-hFSH) vs recombinant human FSH + recombinant human LH (r-hFSH+r-hLH)

Evidence

A Cochrane meta-analysis including 499 women found insufficient evidence to determine if there was a difference in patients treated with r-hFSH+r-hLH compared to those treated with r-hFSH only (4 RCT, OR 1.32, 95% CI 0.85-2.06) (Mochtar et al., 2017). In a subgroup analysis in patients treated with GnRH agonists, although no difference has been observed in live birth rates between the two treatment groups compared (3 RCT, OR 1.73, 95% CI 0.95-3.16, 259 women), a higher probability of ongoing pregnancy has been observed with r-hLH addition (12 RCT, OR 1.27, 95% CI 1.02-1.57, 1980 women). The meta-analysis reported no difference in OHSS rate with r-hLH supplementation to r-hFSH compared to r-hFSH alone (6 RCT, OR 0.38, 95%CI 0.14-1.01, 2178 women). In a subgroup analysis in patients treated with GnRH agonists, a lower probability of OHSS has been observed with r-hLH addition (Mochtar et al., 2017). An RCT, more recent than the meta-analysis, including 238 women also reported

no difference in live birth rate with r-hLH supplementation to r-hFSH (RR 0.78, 95% CI 0.4-1.53) (Lahoud et al., 2017).

In a sub-analysis of the meta-analysis, a small RCT in poor responders showed a beneficial effect of r-hLH pre-treatment to r-hFSH on live birth rate (OR 9.33, 95% CI 1.03-84.20, 43 women) (Ferraretti et al., 2014, Mochtar et al., 2017). However, a large RCT (939 women), more recent than the meta-analysis, reported no effect of r-hLH addition to r-hFSH in Bologna poor responders on live birth rate (10.6% (49/462) vs. 11.7% (56/477)) (Humaidan et al., 2017). In this trial, only one event of mild early OHSS occurred in the r-hFSH+r-hLH group.

A systematic review and meta-analysis focussing on women of advanced age (≥35 years) on the effect of r-hLH supplementation to r-hFSH in fresh IVF cycles included 12 RCTs and 1821 participants (Conforti et al., 2021). Live birth rates were evaluated in only two RCTs, and no differences were detected between ovarian stimulation with r-hLH supplementation and r-hFSH alone (OR 1.53, 95% CI 0.50-4.65, 2 RCT, 371 women). Similarly, no significant differences were seen for clinical pregnancy rate (OR 1.11, 95% CI 0.89-1.38, 11 RCT, 1670 women) and number of oocytes retrieved (MD -0.47, 95% CI -1.07 to + 0.12, 7 RCT, 997 women).

Recommendation

The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for the general IVF population. [2025]	Conditional ⊕⊕◯◯

The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for low responders. [2025]	Conditional ⊕⊕◯◯

The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for women of advanced age (≥35 year). [2025]	Conditional ⊕⊕◯◯

Justification

According to the best available evidence, the combination of r-hFSH with r-hLH results in similar live birth rates compared to r-hFSH alone.

Current evidence from a large RCT in low responders indicated no beneficial effect of the combination of r-hFSH with r-hLH and r-hFSH alone on live birth rate.

Similarly, a systematic review and meta-analysis focussing on women of advanced age (≥35 years) found no evidence of a benefit of adding r-hLH to ovarian stimulation with r-hFSH (Conforti et al., 2021).

The GDG would also like to point to the importance of ‘simplicity of ovarian stimulation’. When comparing compounds, dosages or add-on treatments for ovarian stimulation in this guideline document, preference was always given to the more basic option, unless a clear benefit was shown.

RECOMBINANT (R-HFSH) VS RECOMBINANT HUMAN FSH + HUMAN MENOPAUSAL GONADOTROPIN (HMG)

Evidence

r-hFSH vs. r-hFSH+hMG

An RCT compared the clinical efficacy of highly purified hMG (75 IU) combined with r-hFSH (75-150 IU; n=305) to rFSH alone (150-225 IU; n=305) on ovarian stimulation for IVF in a long GnRHa protocol (Shu et al., 2019). No significant difference was reported between ovarian stimulation with or without hMG supplementation for moderate/severe OHSS (3.3% (10/305) vs. 3.6% (11/305)), clinical pregnancy rate per initiated cycle (29.2% (89/305) vs. 23.9% (73/305)) or number of MII oocytes retrieved (10.6±5.7 vs. 11.4±5.2).

An RCT evaluated whether the addition of hMG (75 IU; n= 78) to rFSH (225-300 IU) during the early follicular phase of ovarian stimulation improves clinical outcomes compared to no supplementation (n=94) in group 4 Bologna poor responders with the long GnRH agonist or GnRH antagonist (97%) protocol (35-44 year) (Qiu et al., 2023). No significant difference was noted with hMG supplementation compared to no supplementation for ongoing pregnancy rate per completed cycle (26.1% (23/88) vs. 27.1% (19/70)) or clinical pregnancy rate per completed cycle (29.5% (26/88) vs. 28.6% (20/70)).

Long-acting rFSH vs. long-acting rFSH + mid-follicular hMG

In an RCT, women underwent ovarian stimulation with long-acting rFSH, in combination with either hCG (150 IU) or hMG (225 IU) starting from day 7 of stimulation until final oocyte maturation in the GnRH antagonist protocol (Decleer et al., 2020). There were no significant differences between hCG and hMG supplementation for live birth rate (fresh+frozen; 11/61 vs. 9/67), clinical pregnancy rate (fresh+frozen; 15/61 vs. 12/67) or number of MII oocytes (6.6±4.4 vs. 6.1±4.8).

An RCT compared the results of two ovarian stimulation protocols for IVF in patients at risk of low ovarian response: long-acting rFSH followed by hMG (300 IU; n=112) versus daily administration of hMG (300 IU; n=109) in a GnRH antagonist protocol (Taronger et al., 2018). There was no difference reported between the hMG/rFSH combination group and hMG only group for cumulative ongoing pregnancy rate and live birth rate (15.2% vs. 22%), ongoing pregnancy and live birth rate per started cycle (15.2% (17/112) vs. 20.2% (22/109)) or cumulative clinical pregnancy rate (19.6% (22/112) vs. 26.6% (29/109)).

Recommendation

The combined use of recombinant FSH (r-hFSH) with human menopausal gonadotropin (hMG), either from the start or mid-phase of ovarian stimulation, is probably not recommended over the use of either r-hFSH or hMG alone in normal and low responders. [2025]	Conditional ⊕⊕◯◯

Justification

From only a handful studies it appears that, adding hMG either in the beginning of the stimulation with rFSH or after a rFSH stimulation period of 5-8 days, does not create any benefits in patients using either the GnRH agonist or antagonist pituitary suppression protocol.

LONG-ACTING VS DAILY RECOMBINANT FSH

Evidence

In a systematic review[13] and meta-analysis, RCTs were included of infertile women undergoing a single IVF/ICSI cycle with either long-acting or a conventional ovarian stimulation protocol based on daily injections (Cozzolino et al., 2019). No significant differences were seen between long-acting and daily rFSH for live birth rate/ongoing pregnancy rate (RR 0.92, 95% CI 0.80–1.05, 8 RCT, 4340 cycles) or incidence of overall OHSS (RR 1.15, 95% CI 0.83-1.57, 5 RCT, 3749 cycles) or moderate/severe OHSS (RR 1.17, 95% CI 0.54-2.56, 4 RCT, 3349 cycles). However, significantly more oocytes were retrieved after ovarian stimulation with the long-acting formulation (MD 1.13, 95% CI +0.33 to +1.92, 5 RCT, 3848 cycles).

In an RCT, 283 women were randomly assigned to either rFSH-CTP (n=142) or rFSH groups (n=141) for ovarian stimulation in a GnRH antagonist protocol for IVF/ICSI (Wu et al., 2025). There was no significant difference in live birth rate (23.2% (33/142) vs. 29% (41/141)) or ongoing pregnancy rate (31.7% vs. 36.9%) when comparing rFSH-CTP to rFSH. No cases of severe OHSS were reported in the rFSH-CTP group compared to 2 in the rFSH group.

In an RCT, 117 women with poor ovarian response were randomly assigned to long-acting (n=59) or daily rFSH (n=58) for ovarian stimulation in a GnRH antagonist protocol for IVF/ICSI (Saharkhiz et al., 2024). The number of MII oocytes retrieved was significantly higher with long-acting rFSH compared to daily rFSH (5.0±2.1 vs. 4.2±1.7). However, there was no statistically significant difference in clinical pregnancy rate between long-acting and daily rFSH (28.8% vs. 22.0%).

Recommendation

The use of long-acting and daily recombinant FSH (rFSH) is equally recommended in GnRH antagonist cycles for normal responders. [2019]	Strong	⊕◯◯◯

Justification

No differences have been observed in several large RCTs and in a small RCT in low responders regarding the probability of pregnancy, or the number of COCs retrieved and the incidence of OHSS.

There are no controlled studies in high responders.

The GnRH antagonist protocol is recommended for the use of long-acting rFSH.

FOLLITROPIN DELTA

Evidence

Follitropin delta requires the use of a dosing algorithm. There are no RCTs comparing individualised follitropin alpha/beta to individualised follitropin delta.

[13] The meta-analysis cited here in the 2019 version of the guideline is replaced by a more recent meta-analysis. The RCT by Kolibianakis *et al.*, 2015 cited here in the 2019 version of the guideline is included in the new meta-analysis and therefore no longer mentioned separately.

Recommendation

Follitropin delta and follitropin alpha/beta are equally recommended for ovarian stimulation. [2025]	Strong ⊕○○○

Justification

Several systematic reviews were published including 3 RCTs and 2682 women, comparing individualised follitropin delta compared to follitropin alfa/beta (Komiya et al., 2024, Nelson et al., 2024, Palomba et al., 2024). The live birth rates and ongoing pregnancy rates were found to be similar between women treated with follitropin delta compared to those treated with follitropin alfa/beta. However, the RCTs included in the systematic reviews include two interventions: a) different follitropin medications, and b) individualised versus fixed dosing. Therefore, it is uncertain that the effect on OHSS rate is due to the gonadotropin or the dosing regimen. Therefore, both gonadotropins are probably equally recommended.

Recombinant (r-hFSH) biosimilar preparations

The section titled recombinant (r-hFSH) biosimilar preparations has been temporarily removed from the guideline while the guideline group conducts a further review of the evidence and conclusions.

Highly purified FSH (hp-FSH) vs human menopausal gonadotropin (hMG)

Evidence

Three RCTs including resp. 20, 80 and 218 women, compared hp-FSH with hMG for ovarian stimulation in the long GnRH agonist protocol and reported similar clinical pregnancy rate (10% (1/10) vs. 10% (1/10); 37.5% (15/40) vs. 45% (18/40) and 34% (35/104) vs. 36% (41/114)) and number of oocytes retrieved (8 (4-11) vs. 13 (4-23); 13.4±0.6 vs. 13.7±0.7 and 8.2±4.7 vs. 9.5±4.83) between both groups (Duijkers et al., 1993, Parsanezhad et al., 2017, Westergaard et al., 1996).

Recommendation

The use of highly purified FSH (hp-FSH) and human menopausal gonadotropin (hMG) for ovarian stimulation in GnRH agonist protocols is equally recommended. [2019]	Conditional ⊕⊕○○

Justification

In patients undergoing OS for IVF/ICSI, the use of hp-FSH does not appear to be preferable over hMG, if downregulation is achieved by GnRH agonists, according to three RCTs.

HUMAN MENOPAUSAL GONADOTROPIN (HMG) VS RECOMBINANT HUMAN FSH + RECOMBINANT LH (R-HFSH+R-HLH)

Evidence

In a small RCT including 122 patients undergoing ovarian stimulation with GnRH agonists, use of r-hFSH+r-hLH was not associated with increased pregnancy rate compared to hMG (28.3% (15/53) vs. 29.3 (17/58)). However, significantly more cycles were cancelled to prevent OHSS in the r-hFSH+r-hLH group compared to the hMG group (11.1% (7/53) vs. 1.7% (1/58)) (Pacchiarotti et al., 2010).

Recommendation

The use of recombinant human LH + recombinant human FSH (r-hFSH+r-hLH) for ovarian stimulation is probably not recommended over human menopausal gonadotropin (hMG) in GnRH agonist protocols with regards to safety. [2019]	Conditional ⊕◯◯◯

Justification

HMG and r-hFSH+r-hLH appear to result in an equal probability of pregnancy in GnRH agonist protocols. However, the risk of OHSS appears to be higher with the use of r-hFSH+r-hLH. The recommendation is not applicable to GnRH antagonist cycles.

GONADOTROPIN COMBINATION WITH HCG

Evidence

In a large RCT, addition of hCG to r-hFSH was investigated in women undergoing their first IVF/ICSI cycle in the long GnRH agonist protocol (Fernández Sánchez et al., 2022). hCG was administered in a fixed daily dose of 1 (n=104), 2 (n=101), 4 (n=99), 8 (n=107), or 12 µg (n=104) daily and compared to a control group receiving placebo (n=104) in 5 different injection volumes to match the injection volume of the different hCG dosages. The incidence of OHSS was lower in the hCG groups compared with the placebo group (2-6 cases per group vs. 12 in the control group) and the risk of OHSS was statistically significantly lower in the 12 µg dose group compared with the placebo group. The ongoing pregnancy rate was significantly lower in the 1 and 2 µg hCG groups compared to placebo (28.4% vs. 29.1% vs. 42.9%). No significant difference was seen with the higher dosages of hCG (4, 8, 12 µg) compared to placebo (39.2% vs. 37.4% vs. 30.4% vs. 42.9%). Significantly less MII oocytes were retrieved in all hCG treatment groups compared to placebo (8.2 vs. 8.3 vs. 8.0 vs. 8.4 vs. 7.3 vs. 9.7).

In an RCT, supplementation with low-dose hCG (100 IU; n=40) to rFSH (200 IU) throughout stimulation was investigated and compared to placebo (n=41) in infertile women (35-40 years) undergoing IVF with a short GnRH agonist protocol (Siristatidis et al., 2022). Three cases of OHSS were noted in the study group (7.5%), compared to one in the control group (2.4%). No significant differences were seen when comparing the study and control groups for clinical pregnancy rate (25% (10/40) vs. 24.4% (10/41)) or number of MII oocytes retrieved (3 (IQR 5) vs. 3 (IQR 2)).

In an RCT, hCG supplementation to r-hFSH (150 IU) from the start of stimulation at different dosages (50 IU, n=15; 100 IU n=16; 150 IU, n=13) was compared to no supplementation (n=16) in the long GnRH agonist protocol (Thuesen et al., 2012). There were no cases of OHSS in the two highest dose groups of hCG, one case of moderate OHSS in the lowest hCG dose group and one case of mild OHSS in the control group. No significant differences were found when comparing the different hCG dosages (50, 100, 150 IU) to no supplementation for cumulative live birth rate per started cycle (33% (5/15) vs. 44% (7/16) vs. 39% (5/13) vs. 31% (5/16)) or live birth rate per started cycle (27% (4/15) vs. 25% (4/16) vs. 31% (4/13) vs. 25% (4/16)).

An RCT investigated whether low-dose hCG added to r-hFSH (n=58) in regimens of ovarian stimulation could improve reproductive outcomes compared to the addition of rLH (n=56) in a GnRH agonist protocol in women aged 36-42 years, entering IVF-ET, especially in those women who had previous IVF failures (Drakakis et al., 2009). Clinical pregnancy rate per protocol was significantly higher with hCG supplementation compared to LH (27.6% (16/58) vs. 10.7% (6/56).

In an RCT, the efficacy of low-dose hCG was investigated using a GnRH antagonist protocol (Koichi et al., 2006). All women were treated with purified urinary FSH (225-300 IU daily) until a follicular diameter of 14 mm was reached. Subsequently, the dose of purified urinary FSH was decreased (75 UI daily) and low-dose hCG (200 IU daily) and GnRH antagonist were initiated in the study group (n=63). In the control group (n=63), the purified urinary FSH dose was increased (300 IU daily) and GnRH antagonist was initiated. One case of severe OHSS was reported in both groups. No significant difference was seen for clinical pregnancy rate (39% (23/59) vs. 36.8% (21/57)).

In an RCT, the efficacy of low-dose hCG was investigated using a GnRH antagonist protocol (Serafini et al., 2006). All women were treated with r-hFSH until a follicular diameter of 14 mm was reached. Subsequently, the dose of purified urinary FSH was decreased (75 UI daily) and low-dose hCG (200 IU daily) and GnRH antagonist were initiated in the study group (n=102). In the control group, the dosage of r-hFSH was continued and GnRH antagonist initiated (n=86). Three cases of OHSS were reported in the study group and four in the control group. No significant differences were reported between the study and control group for clinical pregnancy rate (54.9 (56/102) vs. 40.7% (35/86)) or number of MII oocytes (10.3±0.5 vs. 11.6±0.8).

Low responders

An RCT investigated the effect of late follicular (day 6) supplementation with low-dose hCG (100 IU, n=24 or 200 IU, n=23) on reproductive outcomes and compared them to r-hFSH alone (300 IU, n=26) in poor responder women undergoing ovarian stimulation for ICSI with a GnRH antagonist protocol (Madani et al., 2012). No significant differences were found between the 100 IU and 200 IU hCG groups and control group for live birth rate (14.3% (3/21) vs. 21.1% (4/19) vs. 13% (3/23)), clinical pregnancy rate (19.0% (4/21) vs. 26.3% (5/19) vs. 13% (3/23)) or number of MII oocytes retrieved (5.2±2.1 vs. 5.2±4.4 vs. 3.4±1.7).

In an RCT, the clinical effects of low-dose rhCG (75 IU) supplementation to r-hFSH (600 IU) in the midfollicular phase (n=48) were compared to stimulation with r-hFSH only (600 IU, n=51) in the GnRH agonist protocol for poor responders (Berkkanoglu et al., 2007). No significant differences were found in clinical pregnancy rate per transfer (21.8% vs. 27.1%) or number of MII oocytes retrieved (3.8±0.4 vs. 5.6±0.7) between the r-hFSH and rhCG combination group and the r-hFSH only group.

In an RCT, women underwent ovarian stimulation with long-acting r-hFSH, in combination with hCG (150 IU) starting from day 7 of stimulation until final oocyte maturation in the GnRH antagonist protocol (Decleer et al., 2020). There were no significant differences between hCG supplementation for live birth rate (fresh+frozen; 11/61 vs. 9/67), clinical pregnancy rate (fresh+frozen; 15/61 vs. 12/67) or number of MII oocytes (6.6±4.4 vs. 6.1±4.8).

High responders

In an RCT, the clinical effects of low-dose hCG supplementation from the start of ovarian stimulation with r-hFSH were investigated and compared to no hCG supplementation in PCOS patients in their first IVF/ICSI cycle with freeze-all (Zhu and Fu, 2019). All patients were treated with progesterone (100 mg daily) and hMG (150 IU daily), the study group also received low-dose hCG (200 IU every 3 days). There was no significant difference found between the study and control group for live birth rate per cycle (48.26% (14/29) vs. 35.48% (11/31)), clinical pregnancy rate per transfer (65.52% (19/29) vs. 41.94% (13/31)) or number of MII oocytes retrieved (13.55±6.56 vs. 13.4±6.34).

Recommendation

Adding low dosages of hCG to the FSH stimulation is probably not recommended. [2025]	Conditional ⊕◯◯◯

Justification

No significant benefit was observed for hCG supplementation during ovarian stimulation in the general population, low responders or in the one RCT including women with PCOS. Furthermore, there was large heterogeneity between studies for hCG dosing and timing of initiation.

B. COMBINATIONS OF GONADOTROPINS WITH OTHER STIMULATION DRUGS

LETROZOLE

The combining of the aromatase inhibitor letrozole with gonadotropin during OS has been suggested as a method to reduce the total gonadotropin requirement in IVF. In recent years, the use of letrozole along with gonadotropins has grown, particularly in women predicted to respond poorly to OS (Goswami et al., 2004).

Evidence

Gonadotropin and letrozole combination

High responder

In a small RCT, the effect of letrozole (5 mg) in reducing the risk of OHSS was investigated in women with PCOS (n=27) and compared to placebo (n=28) (Ghasemi Tehrani et al., 2022). All women underwent ovarian stimulation with r-hFSH (150 IU daily) combined with hMG (75 daily) from day 4 of stimulation in the GnRH antagonist protocol. Patients in the study group received letrozole (5 mg) daily

for 5 consecutive days, patients in the control group received placebo in an identical manner. Significantly less cases of moderate OHSS were seen in the letrozole group compared to placebo (1/25 vs. 9/25). No significant difference was seen in clinical pregnancy rate with or without letrozole (60% (15/25) vs. 52% (13/25)).

In an RCT, women with PCOS undergoing ovarian stimulation for ICSI were randomised to either receive combined letrozole (5 mg) and hMG (75 IU) (n=50) or hMG (75-225 IU) and placebo (n=50) in a GnRH antagonist protocol (Lotfy et al., 2022). No significant difference was found between letrozole and placebo supplementation for OHSS (2% (1/50) vs. 10% (5/50), live birth rate (20% (10/50) vs. 28% (14/50)) or clinical pregnancy rate (46.0% (23/50) vs. 52.0% (26/50)).

In an RCT, the clinical outcomes of PCOS patients at very high risk of OHSS undergoing ovarian stimulation with (n=24) or without (n=24) letrozole supplementation (5 mg) to gonadotropins (r-hFSH 150 IU for 6 days followed by hMG 150 IU from day 4) were compared in a GnRH antagonist protocol (Tshzmachyan and Hambartsoumian, 2020). Significantly less cases of OHSS were reported in the study group (2 mild cases) compared to controls (9 mild cases and 1 moderate) (OR 7.86, 95% CI 1.49-41.3). However, live birth rate (33.3% (8/24) vs. 37.5% (9/24) and pregnancy rate per retrieval (58.3% (14/24) vs. 54.2% (13/24)) were comparable with and without letrozole for ovarian stimulation.

In an RCT, it was investigated whether letrozole (2.5 mg daily) supplementation (n=65) to r-hFSH (100-225 IU) stimulation in a GnRH agonist protocol can positively influence the endometrial receptivity compared to conventional stimulation (n=65) in women with an expected high response to ovarian stimulation (Yang et al., 2019). No significant differences were reported with or without letrozole supplementation for incidence of OHSS (0 vs. 1.5% (1/65)) or live birth rate (42.9% (21/49) vs. 62.5% (30/48)).

Normal responder

In an RCT, the impact of letrozole co-treatment (r-hFSH 150 IU + Ltz 5 mg per day; n=67) on reproductive outcomes was investigated in expected normal responders and compared to placebo co-treatment (r-hFSH 150 IU + placebo; n=62) in the GnRH antagonist protocol (Bülow et al., 2022). No significant differences were found between letrozole co-treatment and placebo for live birth rate per woman randomised (24% (19/67) vs. 30% (24/62)), ongoing pregnancy rate per women randomised (26% (21/67) vs. 33% (26/62)) or number of MII oocytes retrieved per protocol (5.8±3.9 vs. 6.6±3.4). Similarly, there was no significant difference in cumulative clinical pregnancy rate after 4.8 years (38% (53/140) vs. 34% (50/147) (Bülow et al., 2022, Bülow et al., 2023).

An RCT compared the IVF outcomes of normal responders who have received gonadotropin both with (n=50) and without (n=50) the addition of letrozole (5 mg/day) from the start of stimulation until final oocyte maturation in the GnRH antagonist protocol (Eftekhar and Saeed, 2020). There was no significant difference with and without letrozole supplementation for incidence of OHSS (4% (2/50) vs. 4% (2/50)). There was also no difference in clinical pregnancy rate (20.0% (10/50) vs. 22.0% (11/50)) or number of MII oocytes retrieved (8.46±4.73 vs. 6.96±4.09) with or without letrozole supplementation.

A small RCT with only 20 patients randomized, investigated the addition of letrozole to FSH in an GnRH antagonist protocol for OS (Verpoest et al., 2006). No significant differences were reported in ongoing pregnancy rate (50% (5/10) vs. 20% (2/10)) or number of oocytes retrieved (13.8±9.2 vs. 9.6±7.7) in the letrozole + FSH group compared to the FSH only group (Verpoest et al., 2006).

A small RCT including 94 women also investigated the addition of letrozole to FSH in an GnRH antagonist protocol for OS (Mukherjee et al., 2012). No differences were reported in clinical pregnancy rate (36% (15/42) vs. 33% (17/52)) or number of mature oocytes (4.6±2.5 vs. 4.9±2.3). There were no cases of OHSS in the letrozole group compared to 7 in the control group (Mukherjee et al., 2012).

In an RCT, 50 women were randomised to receive either FSH-only or FSH combined with letrozole from day 2 until 6 (Yasa et al., 2013). No significant difference in ongoing pregnancy rate was observed with letrozole compared to no letrozole (20% (5/25) vs. 20% (5/25)).

Low responder

A systematic review and meta-analysis[14] compared ovarian stimulation, with a combination of letrozole and gonadotropins to gonadotropins alone in the GnRH antagonist protocol (Qin 2021). The clinical pregnancy rate (per cycle) was not statistically significantly higher with administration of letrozole than that in the control groups (RR 1.57, 95% CI 1.00–2.44, 6 RCT, 564 women). Furthermore, in low- (2.5 mg/day, 5 days) or high-dose (5 mg/day, 5 days) subgroups, no significant differences were indicated in the clinical pregnancy rate with administration of letrozole compared to that in the control groups (RR 1.65, 95% CI 0.85–3.18, 3 RCT, 270 women; RR 1.5, 95% CI 0.82–2.73, 3 RCT, 294 women).

One RCT was found comparing the addition of letrozole with the addition of CC to gonadotropins in an GnRH antagonist protocol in 184 poor responder women and reported no significant difference in clinical pregnancy rate between groups (11.3% (9/87) vs. 8% (7/80)) (Eftekhar et al., 2014).

Recommendation

The addition of letrozole to gonadotropins in stimulation protocols for predicted high responders is probably not recommended. [updated]	Conditional ⊕◯◯◯

The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders. [2019]	Conditional ⊕◯◯◯

The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted low responders. [2019]	Conditional ⊕⊕◯◯

Justification

Due to the small number and size of RCTs available, no solid recommendation can be made for letrozole substitution of gonadotropins.

Addition of letrozole to FSH in an GnRH antagonist protocol does not improve efficacy of OS in high, normal or low responders. The use of letrozole may reduce the risk of OHSS, however this was only shown in two small RCTs in high responders.

With regard to safety, although manufacturer warnings persist due to early preclinical concerns, multiple systematic reviews and meta-analyses consistently demonstrate no significant increase in congenital malformations with letrozole compared to clomiphene citrate, natural conception, or gonadotropins, with some cohort studies even suggesting a reduced risk (Pundir et al., 2021, Sharma et al., 2014, Tulandi et al., 2006). Large registry-based studies and retrospective cohorts reinforce these

[14] The meta-analysis by Bechtejew *et al.*, 2017 has been replaced by a more recent meta-analysis. The RCT by Ebrahimi *et al.*, 2017 described here in the 2019 version of the guideline is included in the meta-analysis and therefore no longer described separately.

findings, showing comparable rates of major and minor anomalies across treatment groups (Takeshima et al., 2022, Tatsumi et al., 2017). Nonetheless, the off-label nature of letrozole use requires appropriate informed consent.

CLOMIPHENE CITRATE

Evidence

Gonadotropin and clomiphene citrate combination

High responder

In an RCT, women with PCOS undergoing ovarian stimulation for ICSI were randomised to either receive combined clomiphene citrate (CC) (5 mg) and hMG (75 IU) (n=50) or hMG (75-225 IU) and placebo (n=50) in a GnRH antagonist protocol (Lotfy et al., 2022). No significant difference was noted for OHSS rate (0 vs. 10% (5/50)), live birth rate (24% (12/50) vs. 28% (14/50)) or clinical pregnancy rate (48% (24/50) vs. 52.0% (26/50)) between clomiphene and placebo supplementation.

In the prospective study by Saleh *et al.* (including 128 PCOS patients) the study group received a stimulation protocol consisting of CC, combined with a GnRH antagonist and r-hFSH, compared to GnRH antagonist with r-hFSH in the control group (Saleh et al., 2014). There was no significant difference in the clinical pregnancy rate (43.8% vs. 45.3%), number of oocytes retrieved (7.7± 1.3 vs. 8.1± 1.4) or number of mature oocytes (5.7± 1.1 vs. 6.1 ±1.3) between the study group and the control group (Saleh et al., 2014).

In the retrospective study by Jiang *et al.* (174 PCOS patients) the study group received a stimulation protocol consisting of CC combined with progestin protocol (MPA) and hMG, compared to MPA with hMG in the control group (Jiang and Kuang, 2017). There were significantly more oocytes retrieved (13 (0–42) vs. 5 (0–30)) and mature oocytes (11 (0–35) vs. 4 (0–26)) in the control group as compared to the study group. There were no cases of moderate or severe OHSS in either group (Jiang and Kuang, 2017).

Normal responder

A systematic review and meta-analysis[15] investigated efficacy of ovarian stimulation with a combination of CC and reduced dose gonadotropins compared to conventional stimulation without oral medication (Datta et al., 2021). No significant difference was found between stimulation with CC and conventional gonadotropin stimulation for live birth rate (RR 0.88, 95 % CI 0.69-1.12, 3 RCTs, 573 women). However, the risk of OHSS was significantly lower with the use of CC supplementation compared to the conventional (RR 0.12, 95% CI 0.03-0.51, 3 RCTs, 623 women).

In an RCT, the effect of ovarian stimulation with (n=144) or without (n=132) clomiphene citrate (50 mg) supplementation to hMG stimulation (150 IU) was investigated in normal ovulatory women undergoing IVF/ICSI with the progestin-primed stimulation protocol (Liu et al., 2018). No significant differences were seen when comparing ovarian stimulation with or without clomiphene citrate for cumulative ongoing pregnancy rate per patient (60.6% (97/160) vs. 53.1% (85/160)), cumulative clinical pregnancy

[15] A more recent meta-analysis was found with the literature update of 2024, therefore the meta-analysis by Bechtejew *et al.*, 2017 was removed.

rate per patient (68.8% (110/160) vs. 66.9% (107/160)) or number of MII oocytes retrieved (8.71±5.28 vs. 8.9±6.59).

Low responder

A systematic review and meta-analysis[16] compared ovarian stimulation with a combination of clomiphene citrate and gonadotropins to gonadotropins alone, both in the GnRH agonist and antagonist protocol (Montoya-Botero et al., 2021). There was no significant difference in the clinical pregnancy rates (CC+GnRH antagonist vs conventional stimulation in GnRH agonist: RR 1.00, 95% CI 0.96-1.04, 4 RCT, 1228 women; CC+GnRH antagonist vs conventional stimulation in GnRH antagonist: RR 1.00, 95% CI 0.93-1.08, 1 RCT, 77 women) or number of oocytes retrieved with clomiphene supplementation in the GnRH antagonist protocol versus conventional stimulation in the GnRH agonist protocol (MD -0.45, -1.49 to 0.59, 5 RCT, 1239 cycles) or conventional stimulation in the GnRH antagonist protocol (MD -0.59, -1.42 to 0.24, 1 RCT, 77 cycles).

An RCT not included in the meta-analysis, also investigated the combination of CC and gonadotrophins in an antagonist protocol in 250 poor responders. A significantly lower clinical pregnancy rate (5.9% vs. 14.1%) was reported with CC addition compared to no CC, which was not associated with a difference in the number of oocytes retrieved (3.8 ± 2.9 vs. 3.41±1.9) (Schimberni et al., 2016).

Gonadotropin substitution by clomiphene citrate

Studies comparing CC with the standard of care (FSH ovarian stimulation) are very scarce. We did not retrieve any RCTs comparing clomiphene citrate (CC) alone in high responders.

Normal responder

One cohort study was identified, including 25 'good prognosis patients', comparing a protocol with clomiphene citrate addition to GnRH antagonist protocol. Significantly less oocytes were retrieved with the CC addition protocol (6.4±0.7 vs. 10.7±0.9). However, there was no difference in clinical pregnancy rate between CC addition and GnRH antagonist protocol (27.3% (6/22) vs. 49.0% (24/49) (Zander-Fox et al., 2018).

Low responder

Only one RCT, including 249 poor responder women, has compared CC with a short GnRH agonist FSH protocol and showed similar live birth rate (5/145 vs. 7/146; RR 0.72, 95% CI 0.23-2.21) (Ragni et al., 2012).

Conclusion

There is insufficient evidence available to recommend the substitution of FSH by Clomiphene Citrate in ovarian stimulation.

Recommendation

The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted high responders. [2019]	Conditional ⊕⊕◯◯

[16] The meta-analysis by Bechtejew *et al.*, 2017 has been replaced by a more recent meta-analysis.

The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders. [2025]	Conditional	⊕⊕⊕◯

Clomiphene citrate alone or in combination with gonadotrophins, and gonadotropin stimulation alone are probably equally recommended for predicted low responders. [updated]	Conditional	⊕⊕◯◯

Justification

In women with normal ovarian response, current evidence shows no benefit in terms of efficacy with CC supplementation to gonadotropins. The systematic review reported a significantly lower OHSS rate, however, this is due to the lower dose of gonadotropins that was used in the CC and gonadotropins combination arm.

In women with low ovarian response, no differences were reported in terms of safety and efficacy between CC alone, CC in combination with gonadotropins or gonadotropin stimulation alone.

In women with high ovarian response, limited evidence shows no benefit of CC supplementation to gonadotropins in terms of efficacy.

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7. Adjustment of gonadotropin dose

PICO Question: Is adjustment of the gonadotropin dosage during the stimulation phase meaningful in terms of efficacy and safety?

A systematic review studied the incidence of dose adjustments in clinical trials (Fatemi et al., 2021). Eighteen RCTs out of 1073 RCTs investigated were identified that reported dose adjustments: in 10 RCTs (3952 cycles), dose increases were reported, in 11 RCTs (5123 cycles), dose reductions were reported and five RCTs reported unspecified dose changes (1359 cycles). However, the systematic review was unable to provide evidence of the impact of gonadotropin dose adjustments on clinical outcomes. These results are in agreement with a real-world study reporting on 33,962 ovarian stimulation cycles (23,582 patients), of which 40.7% had at least one dose adjustment. Among cycles with dose changes, 57.4% had at least one dose increase, 62.5% had at least one dose decrease, and 19.9% of cycles included both increases and decreases (Mahony et al., 2021).

Evidence

An RCT investigated the effect of a modified flexible GnRH antagonist protocol by reducing r-hFSH dose by 30-50% as soon as the leading follicles reached 14 mm. Additionally, the GnRH antagonist administration was suppressed on final oocyte maturation day in the study group. The control group underwent a conventional flexible GnRH antagonist protocol (Xu et al., 2024). Comparing the modified to the conventional flexible GnRH antagonist protocol, a significantly higher live birth rate (38.1% (104/273) vs. 27.5% (75/273); RR 1.39 (1.09-1.77)) was seen. No significant differences were noted in risk of OHSS (1.1% (3/273) vs. 1.8% (5/273)) or number of MII oocytes (10.95±4.43 vs. 10.75±4.53)) between the modified and conventional GnRH antagonist protocol.

Another RCT investigated the effect of reducing the r-hFSH dose as soon as ≥ 3 follicles ≥ 14 mm were present until the criteria for final oocyte maturation were met (Lawrenz et al., 2021) and compared to conventional r-hFSH dosing. No significant difference was found in number of MII oocytes between the dose reduction group and the conventional dosing group (Lawrenz et al., 2021).

An RCT including 151 women compared increasing hMG dose (with 75 IU) on the day of GnRH antagonist initiation with not increasing hMG dose and reported no difference in clinical pregnancy rate (36.2% vs. 32.1%, OR 1.3, 95% CI 0.63-2.6) or number of oocytes retrieved (9.2±2.1 vs. 10.1±3.8) between both groups (Aboulghar et al., 2004).

A more recent retrospective study reported that changing the dose of gonadotropins during stimulation (increasing or decreasing) had no effect on clinical or ongoing pregnancy rates. Clinical pregnancy rate was 28.2% (11/39) with dose increase vs. 32.1% (27/84) with dose decrease vs. 25.8% (110/427) with no dose adjustments. Similarly, ongoing pregnancy rate was resp. 23.1% (9/39) vs. 25.0% (21/84) vs. 22.5% (96/427) (Martin et al., 2006).

Two RCTs investigated the effect of gonadotropin dose modulation in poor responder patients. Van Hooff *et al.* investigated the effect of doubling hMG dose on day 6 of OS in 47 low responders and reported no difference in pregnancy rate (2/25 vs. 1/22) or number of oocytes retrieved (4.7±1.0 vs. 4.6±0.8). No cases of severe OHSS were reported (van Hooff et al., 1993). A more recent RCT including 73 poor responders investigated the effect of reducing gonadotropin dose (step-down FSH protocol: 450 IU starting dose, reduced to 300 IU/d when serum E2 values reached 200 pg/mL and again reduced

to 150 IU/d when 2 follicles of 12 mm in diameter were detected on ultrasound) during OS and reported no difference in number of pregnancies (3/34 vs. 4/39) or number of oocytes retrieved (6.4±0.6 vs. 6.3±0.6) (Cedrin-Durnerin et al., 2000).

Aboulghar *et al.* investigated the effect of reducing hMG dose before coasting in 49 women at risk for developing OHSS. They found that reducing the hMG dose before coasting compared to not reducing hMG dose significantly reduced the duration of coasting (1.8±0.65 vs. 2.92±0.92 days) without influencing pregnancy rate (33.3% (8/25) vs. 35% 7/24) (Aboulghar et al., 2000).

Recommendation

Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during ovarian stimulation is probably not recommended. [2019]	Conditional ⊕◯◯◯

Given the lack of evidence on the value of dose adjustments during ovarian stimulation, it is important that the gonadotropin starting dose is appropriate based on patient characteristics and desired outcome. [2025]	GPP

Justification

It is considered good practice to use ovarian reserve testing, patient preferences etc to determine the appropriate gonadotropin starting dose. The current evidence does not support changing gonadotropin dose during OS in the mid-stimulation phase. Modification (higher or lower) of gonadotrophin dose during ovarian stimulation for IVF/ICSI does not influence pregnancy rate. There is no evidence regarding dose modifications before the mid-stimulation phase during OS.

The RCT by Xu *et al.* and Lawrentz *et al.* are not specifically addressing the question, however, it is the best evidence found (Lawrenz et al., 2021, Xu et al., 2024).

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8. Adjunct therapies

PICO Question: Is the addition of adjuncts in ovarian stimulation meaningful in terms of efficacy and safety?

Metformin

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant metformin compared to control or placebo were considered for inclusion to address the efficacy and safety of metformin use during ovarian stimulation in IVF/ICSI treatment. All studies addressing the role of adjunct metformin were in women with PCOS.

A Cochrane systematic review and meta-analysis[17] found no conclusive evidence that metformin before or during ovarian stimulation improves live birth rate compared to placebo/no treatment in women with PCOS (Tso et al., 2020). Substantial heterogeneity was found between studies, therefore the results were analysed based on the type of ovarian stimulation protocol. Six RCTs compared metformin to placebo/no treatment in a long GnRH agonist protocol, pooling of these RCTs showed no statistically significant evidence of improvements in live birth rate with metformin (OR 1.30, 95% CI 0.94-1.79, 651 women). One RCT compared metformin to placebo/no treatment in a GnRH antagonist protocol and showed that metformin may reduce the live birth rate compared to placebo/no treatment (OR 0.48; 95% CI 0.29-0.79, 153 women). A lower incidence of OHSS (severity of OHSS not specified) was found in the metformin group as compared to placebo/no treatment (11 RCT, RR 0.46; 95% CI 0.29-0.72, 1091 women). The majority of the studies in the meta-analysis involved the use of GnRH agonist and only two studies used the GnRH antagonist protocol. Subgroup analysis based on the type of GnRH analogue showed only a significant difference in OHSS between the metformin group compared to control group when used with a long GnRH agonist protocol (9 RCT, OR 0.40, 95% CI 0.26-0.60), not with a GnRH antagonist protocol (2 RCT, OR 0.97, 95% CI 0.32-2.98, 193 women). The Cochrane meta-analysis also showed no significant difference in number of oocytes retrieved in the metformin compared to control group (11 RCT, MD 0.03; 95% CI -1.42 to 1.48) (Tso et al., 2020).

An RCT, more recent than the Cochrane review, included 320 PCOS women randomised to receive either metformin (n=160) or placebo (n=160) during ovarian stimulation for IVF in a GnRH antagonist protocol (Hussein et al., 2021). This RCT reported that women receiving metformin had a significantly higher live birth rate (38.1% (61/160) vs. 27.5% (44/160) compared to placebo. One case of severe OHSS was reported in each group.

Another RCT (102 PCOS women), not included in the Cochrane review, of metformin compared to placebo in an GnRH agonist protocol, reported no significant difference in live birth rate (25.5% (13/51) vs. 17.6% (9/51)) with adjuvant metformin compared to placebo treatment. However, significantly less oocytes were retrieved in the metformin group compared to placebo (9.06±4.23 16.86±8.3) (Abdalmageed et al., 2019).

[17] The Meta-analysis by Tso *et al.* 2014 was replaced by the updated version. Jacob *et al.*, 2016 is included in the updated meta-analysis and therefore no longer mentioned separately.

Recommendations

Routine use of adjuvant metformin before and/or during ovarian stimulation is probably not recommended when using the GnRH antagonist protocol for women with PCOS. [updated]	Conditional	⊕⊕◯◯

Justification

The GDG recommends the use of GnRH antagonist for high responders and in women with PCOS. As current evidence does not show a beneficial effect of routine use of metformin in reducing OHSS when used with GnRH antagonist protocols and given the inconsistent evidence for live birth outcome, metformin is probably not recommended in women with PCOS.

GROWTH HORMONE (GH)

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant growth hormone (GH) compared to control or placebo were considered for inclusion to address the efficacy and safety of GH use during ovarian stimulation in IVF/ICSI treatment.

Dose and administration of GH that was administered varied among studies from 4-12 IU subcutaneously daily to 4-24 IU on alternate days. The timing of GH administration varied between trials from daily administration pre-stimulation to alternate doses after the start of stimulation.

GH for normal responders

A Cochrane meta-analysis including 80 women considered as normal responder undergoing IVF treatment reported no significant difference in live birth rate (2 RCT, OR 1.32, 95% CI 0.40–4.43) with routine use of GH in women undergoing IVF treatment compared to placebo (Duffy et al., 2010). The updated Cochrane systematic review and meta-analysis included the same two RCTs in women considered as normal responders (Sood et al., 2021).

An RCT included 288 normal responder women randomised to receive either GH adjunct therapy (n=144) compared to no adjunct treatment (n=144) in a GnRH antagonist protocol (Mourad et al., 2025). There was no significant difference observed between adjunct GH treatment and no adjunct treatment for live birth rate after fresh transfer (32% (25/78) vs. 33% (30/90)) or clinical pregnancy rate after fresh transfer (44% (34/78) vs. 50% (45/90)). In addition, no significant difference was observed in the number of MII oocytes retrieved (8.5±6.2 vs. 8.6±6.3, ITT).

GH for low responders

A systematic review and meta-analysis[18] investigated the effect of growth hormone supplementation on reproductive outcomes in women experiencing a poor ovarian response to stimulation (Liu et al., 2025). Comparing women receiving GH treatment to women receiving placebo/no treatment, a significantly higher live birth rate (OR 1.80, 95% CI 1.22-2.64, 9 RCTs, 945 women) and clinical pregnancy

[18] The meta-analysis by Li *et al.*, 2017 is replaced by the more recent Cochrane meta-analysis. The RCT by Choe *et al.*, 2018 is included in this meta-analysis and therefore no longer mentioned separately.

rate (OR 1.92, 95% CI 1.51-2.43, 19 RCTs, 1763 women) was observed. Furthermore, significantly more MII oocytes were retrieved in women receiving GH treatment (MD 1.63, 95% CI 1.13-2.13, 11 RCTs, 1358 women).

GH for PCOS

An RCT investigated the effect of GH supplementation on reproductive outcomes in women with PCOS (Gong et al., 2020). No significant difference was found in clinical pregnancy rate between women with GH treatment versus controls (54% (27/50) vs. 42% (21/50)) or number of MII oocytes (12.30±6.80 vs. 10.02±6.48).

Recommendations

Use of adjunct growth hormone before and/or during ovarian stimulation is not recommended for normal responders. [2025]	Strong	⊕◯◯◯
Use of adjunct growth hormone before and/or during ovarian stimulation is probably not recommended for low responders. [updated]	Conditional	⊕◯◯◯
Use of adjunct growth hormone before and/or during ovarian stimulation is not recommended for women with PCOS. [2025]	Strong	⊕⊕◯◯

Justification

In general, there was a lack of data showing a beneficial effect. It is of great importance to point out that GH has the potential for serious harm and no long-term safety data are available. Furthermore, GH dosing schemes were very heterogenous. One new RCT in normal responders showed no benefit and the conclusion of the updated Cochrane review (Sood et al., 2021) was similar to the previous one (Duffy et al., 2010). Collective evidence from 2 small RCTs (included in meta-analysis by Duffy *et al.*) reported no effect on live birth rate (Duffy et al., 2010). One RCT involving women with PCOS showed no improvement in live birth rates following GH supplementation (Gong et al., 2020). There is collective evidence from the updated Cochrane review (Sood et al., 2021) and confirmed in the most recent meta-analysis (Liu et al., 2025) that adjuvant GH before and/ or during ovarian stimulation improves live birth rates in low responders following IVF treatment. Similar results were also reported by older meta-analysis (Duffy et al., 2010, Kolibianakis et al., 2009, Kyrou et al., 2009, Li et al., 2017). Despite the possible beneficial effects in low responders on live birth rate, the evidence is of too limited quality to recommend GH during OS. The studies in the systematic review were generally underpowered and the definition of low response very heterogenous among studies. The GDG encourages further research on the use and dosing of GH in low responders, focussing on long-term safety data, both in the woman and offspring.

TESTOSTERONE

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant testosterone pre-treatment compared to control or placebo were considered for inclusion to address the efficacy and safety of pre-treatment testosterone during ovarian stimulation in IVF/ICSI treatment. All studies addressing the role adjuvant testosterone were in predicted low responders.

Testosterone was administered transdermally, mostly as gel. Duration and dose of testosterone pre-treatment was either 12.5 mg/day of testosterone gel during pituitary downregulation, or testosterone gel 1%, with varying dose between studies between 10 mg/day to 12.5 mg/day preceding gonadotropin stimulation. Duration varied between studies ranging from 10-56 days.

A Cochrane systematic review and meta-analysis[19] studied the effect of testosterone pre-treatment versus placebo/no treatment (Naik et al., 2024). A significantly higher live birth rate/ongoing pregnancy rate was found in women pretreated with transdermal testosterone compared with those who were not (OR 2.53, 95% CI 1.61-3.99, 8 RCT, 716 women).

In an RCT, 120 poor responder women were randomly assigned to receive methyltestosterone (n=60) or placebo pre-treatment (n=60) before ovarian stimulation for IVF/ICSI (Aliakbar et al., 2024). There was no significant difference in ongoing pregnancy rate (13.3% (8/60) vs. 3.3% (2/60)) or clinical pregnancy rate (15% (9/60) vs. 6.67% (4/60)) with testosterone pre-treatment compared to placebo.

In a pilot RCT, not included in the meta-analysis, testosterone treatment administered during ovarian stimulation in women experiencing poor ovarian response (Saharkhiz et al., 2018) showed that the pregnancy rate was significantly higher in the treatment group compared to controls (16% (4/25) vs. 0% (0/23). Number of oocytes was also significantly higher in the study group vs controls (2.48±1.64 vs. 1.17±1.27).

Recommendations

Use of testosterone before ovarian stimulation is probably not recommended for low responders. [updated]	conditional ⊕⊕⊕◯

Justification

There is currently inconsistent evidence that testosterone pre-treatment before ovarian stimulation improves ovarian response in terms of number of oocytes retrieved and clinical outcomes of live birth rates in low responders undergoing IVF treatment. Also, due to insufficient data on dosage, administration duration and safety we cannot recommend testosterone use until a large RCT has been conducted.

[19] The Cochrane systematic review and meta-analysis by Nagels *et al.*, 2015 was replaced by a more recent systematic review. The RCTs by Kim *et al.*, 2014 and Bosdou *et al.*, 2016 are included in this meta-analysis and therefore no longer mentioned separately.

DEHYDROEPIANDROSTERONE (DHEA)

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant Dehydroepiandrosterone (DHEA) compared to control or placebo were considered for inclusion to address the efficacy and safety of DHEA use during ovarian stimulation in IVF/ICSI treatment.

The dose of DHEA used was 75 mg/day and varied in duration, starting either 6, 8 or 12 weeks before the start of ovarian stimulation and continued during ovarian stimulation. Most studies started DHEA 12 weeks prior to ovarian stimulation.

A systematic review and meta-analysis[20] investigated the effects of DHEA priming in women undergoing ovarian stimulation for IVF/ICSI (Huang et al., 2025). No significant difference was found between DHEA treatment or placebo/no treatment in live birth rate (OR 1.33, 95% CI 0.98-1.82, 10 RCTs, 1217 women). DHEA pre-treatment did also not increase the number of MII oocytes retrieved (MD 0.56, CI -0.06 to 1.18, 8 RCTs, 842 women).

Recommendations

Use of DHEA before and/or during ovarian stimulation is not recommended for low responders. [updated]	Strong	⊕⊕◯◯

Use of DHEA before and/or during ovarian stimulation is not recommended for normal responders. [2025]	Strong	⊕⊕◯◯

Justification

The systematic review including 16 RCTs showed that adjuvant DHEA use before and during ovarian stimulation does not improve live birth/ongoing pregnancy rate (Huang et al., 2025). Two RCTs involving normal responders showed that DHEA use before and during ovarian stimulation did not improve clinical pregnancy rates and number of oocytes retrieved (Mostajeran et al., 2018, Yeung et al., 2016). The studies varied in duration of DHEA treatment, possibly contributing towards the inconsistence in observed results. Also, due to insufficient data on administration duration and safety we cannot recommend DHEA use until a large RCT has been conducted.

ASPIRIN

Evidence

To address the efficacy and safety of adjuvant aspirin use with ovarian stimulation in IVF/ICSI treatment, studies were selected if aspirin was used before and/ or during ovarian stimulation. Studies commencing

[20] The Cochrane systematic review and meta-analysis was replaced by a more recent systematic review. The RCTs by Kotb *et al.*, 2016, Narkwichean *et al.*, 2017, Mostajeran *et al.*, 2018 and Yeung *et al.*, 2016 are included in this meta-analysis and therefore no longer mentioned separately.

aspirin after ovarian stimulation were excluded. Systematic reviews, meta-analyses and eligible RCTs (not included in the selected systematic reviews or meta-analyses) comparing adjuvant aspirin alone (without other co-interventions) compared to control or placebo were included.

Doses of aspirin used in the studies varied between 75 mg daily, 80 mg daily or 100 mg daily and aspirin was continued until hCG administration for final oocyte maturation, 12 weeks of pregnancy or until delivery.

A Cochrane meta-analysis combining 3 RCTs with 1053 women reported no significant difference in the live birth rate (3 RCT, RR 0.91, 95% CI 0.72-1.15) or ongoing pregnancy rate (2 RCT, RR 0.94, 95% CI 0.69-1.27) between the aspirin and control group (Siristatidis et al., 2016). Due to technical limitations of the meta-analysis to specifically address the role of adjuvant aspirin use before and/or during ovarian stimulation, all other outcomes were assessed from individual studies.

Results from 4 RCTs in the general IVF/ICSI population showed that adjuvant aspirin has no beneficial effect on the number of oocytes retrieved (Table 7) (Dirckx et al., 2009, Lambers et al., 2009, Moini et al., 2007, Pakkila et al., 2005). One RCT, Rubinstein *et al.* reported a significantly higher number of oocytes with aspirin compared to placebo treatment (16.2±6.7 vs. 8.6±4.6) (Rubinstein et al., 1999).

There was one RCT including poor responders which demonstrated no significant difference in number of oocytes retrieved and clinical pregnancy rate between the aspirin compared to control group (Lok et al., 2004).

An RCT investigated the effect of pre-treatment with low-dose aspirin on the risk of OHSS in the long GnRH agonist protocol in 232 women with PCOS (Namavar Jahromi et al., 2019). No significant difference was found between aspirin and placebo pre-treatment for moderate to severe OHSS (34.9% (38/109) vs. 34.9% (38/109)) and clinical pregnancy rate (28.4% (31/109) vs. 22.9% (24/105)).

Table 8: Number of oocytes retrieved.

Study	Cohort (n)	Aspirin	Placebo
Dirckx 2009	193	12.6 ± 7.6	12.9 ± 7.9
Lambers 2009	169	13.7	13.5
Moini 2007	145	6.9 ± 5.6	8.6 ± 6.8
Pakkila 2005	374	12.0 ± 7.0	12.7 ± 7.2
Lok 2004	60	3.0 (2.0–7.25)	4.0 (3.0–7.25)
Rubinstein 1999	298	16.2 ± 6.7	8.6 ± 4.6

Recommendation

Use of aspirin before and/or during ovarian stimulation is not recommended in the general IVF/ICSI population nor for low responders. [2019]	Strong	⊕⊕⊕◯

Justification

The existing evidence suggests that adjuvant aspirin before and/ or during ovarian stimulation does not improve ovarian response in terms of number of oocytes retrieved and clinical outcomes of clinical or ongoing pregnancy, or live birth rates following IVF treatment.

Evidence could not be formulated on the outcome of OHSS due to poor study quality and reporting method (Varnagy et al., 2010).

INDOMETHACIN

Evidence

Current evidence is limited to one case report (Nargund and Wei, 1996).

Conclusion

There are no controlled studies nor RCTs addressing the efficacy and safety of adjuvant indomethacin use during ovarian stimulation in IVF treatment. Thus, there is no evidence to recommend the use of indomethacin during OS.

SILDENAFIL

Sildenafil is used in ovarian stimulation to increase ovarian vascularization and hence increase live birth.

Evidence

Studies on sildenafil administered (for improving endometrial thickness) after oocyte pick-up were not included.

A small RCT evaluated the effect of vaginal sildenafil during ovarian stimulation on IVF success rate in 72 women (Tehraninejad et al., 2018). No significant difference was found between the study group and the control group for clinical pregnancy rate (33.3% (12/36) vs. 27.8% (10/36)).

A small pseudo-randomised RCT including 60 patients classified as poor responders reported no significant difference in the clinical pregnancy rate (16.7% (5/30) vs. 13.3% (4/30)) or number of oocytes retrieved between the sildenafil and control group (3.95±1.40 vs. 3.65± 1.14) (Ataalla et al., 2017).

Recommendations

Use of sildenafil before and/or during ovarian stimulation is not recommended for low responders. [2019]	Strong	⊕◯◯◯

Justification

Current evidence from one low-quality, pseudo-randomized study involving women considered as low responders undergoing IVF showed no improvement in ovarian response with adjuvant sildenafil use during ovarian stimulation. Furthermore, a Dutch trial using sildenafil to try to correct foetal growth restriction (STRIDER study) has been halted after 11 babies subsequently died (Ganzevoort et al., 2014, Hawkes, 2018).

ANTI-OXIDANTS (MYO-INOSITOL)

Evidence

A Cochrane systematic review and meta-analysis investigated the effect of inositol on IVF outcomes in women with PCOS (Showell et al., 2018). The start and duration of pre-treatment varied between eight to twelve weeks before IVF/ICSI treatment. The treatment period for one study lasted from the first day of the cycle to 14 days after embryo transfer, and another study started treatment on the first day of GnRH agonist administration. No significant difference in live birth rates have been found with myo-inositol compared to standard treatment (folic acid) (2 RCT, OR 2.42; 95% CI 0.75-7.83; 84 women).

An RCT investigated the effect of myo-inositol pre-treatment on pregnancy outcomes in 60 women referred for IVF (Seyedoshohadaei et al., 2022). Live birth rate was significantly higher in women receiving myo-inositol pre-treatment compared to standard treatment (folic acid) (26.7% (8/30) vs. 10% (3/30)). Similarly, clinical pregnancy rate (56.7% (17/30) vs. 23.3% (7/30)) and the number of MII oocytes (7.53±3.71 vs. 5.43±2.50) were higher in the study group compared to controls.

An RCT investigated the effect of myo-inositol treatment before and during ovarian stimulation on IVF outcomes in non-PCOS women (Lisi et al., 2012). There was no significant difference in clinical pregnancy rate between myo-inositol treatment and standard treatment (folic acid) (28% (14/50) vs. 24% (12/50)). However, significantly less MII oocytes were retrieved after myo-inositol treatment compared to standard treatment (4.8±2.2 vs. 6.3±2.9).

Two RCTs investigated the effect of myo-inositol treatment before and during ovarian stimulation on reproductive outcomes in respectively 60 and 112 women experiencing poor ovarian response to stimulation (Mohammadi et al., 2021, Nazari et al., 2020). No significant differences were found between women receiving myo-inositol and women receiving standard treatment (folic acid) for ongoing pregnancy rate (7.1% vs. 3.6%) (Nazari et al., 2020), clinical pregnancy rate (6.6% (2/30) vs. 0% (0/30)) or number of MII oocytes (2.36±1.64 vs. 1.87±1.07) (Mohammadi et al., 2021).

Recommendations

Use of myo-inositol before and/or during ovarian stimulation is probably not recommended for women with PCOS undergoing IVF. [2025]	Conditional	⊕◯◯◯
Use of myo-inositol before and/or during ovarian stimulation is not recommended in low responders. [2025]	Strong	⊕⊕◯◯
Use of myo-inositol before and/or during ovarian stimulation is not recommended in non-PCOS women undergoing IVF. [2025]	Strong	⊕⊕◯◯

Justification

Studies varied in the duration of pre-treatment and timing of myo-inositol treatment. The Cochrane review concluded that it is uncertain whether myo-inositol improves live birth rates in women undergoing IVF (Showell et al., 2018). An RCT involving non-PCOS women undergoing IVF showed no improvement in clinical pregnancy rates but a lower number of MII oocytes in the myo-inositol group (Lisi et al., 2012). Two RCTs involving low responders undergoing IVF showed no improvement in the pregnancy rates and number of MII oocytes in the myo-inositol group (Mohammadi et al., 2021, Nazari et al., 2020). For non-PCOS women and low responders, there is no biological rational for using myo-inositol to the treatment scheme.

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9. Non-conventional start of ovarian stimulation

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

Non-conventional start

Evidence

A retrospective study in 150 normal responders reported comparable ongoing pregnancy rates (39.4% (13/33) vs. 33.3% (12/36) vs. 39.0% (16/41)) and number of oocytes retrieved (6.6±3.8 vs. 5.9±4.3 vs. 5.9±4.2) when stimulation was started in the late follicular or luteal phase as compared to conventional start (day 2-5) (Qin et al., 2016). Similarly, a more recent, large retrospective study in 1302 normal responders (non-oncologic fertility preservation) reported no difference in number of oocytes retrieved (12.7±2.7 vs. 13.0±3.1 vs. 13.2±2.9 vs. 13.1±2.3) between early follicular (day 4-7), late follicular (> day 7), and luteal start stimulation as compared to conventional start (day 2/3) (Pereira et al., 2017).

Recommendation

Random-start ovarian stimulation could be used when a fresh transfer is not intended; nonetheless, the risk of OHSS in case of concurrent spontaneous conception should always be discussed with the patient [Reworded]	GPP

Justification

Current evidence in normal responders reported no difference in efficacy in terms of number of oocytes retrieved with non-conventional start stimulation as compared to conventional (early follicular) start stimulation. This validates the feasibility of random-start protocols; however, freeze-all oocytes or embryos is mandatory. A medico-economic study is needed as non-conventional stimulation might require a higher consumption of FSH and the long-term child health has to be carefully monitored as the hormonal environment of the oocytes is modified. The risk of an undetected, natural conception pregnancy in non-conventional start stimulation is low (Lawrenz et al., 2024), however, they could lead to severe OHSS and hospitalisation (Semrl et al., 2024).

Luteal phase stimulation

Luteal phase stimulation can be regarded as an extension to urgent oncologic fertility preservation. A distinction must be made between gonadotropin pre-treatment in the luteal phase before follicular stimulation with fresh transfer, and ovarian stimulation in the luteal phase (day 15-19) with mandatory frozen oocytes/embryos.

Evidence

Late luteal gonadotropin start with intention of fresh transfer

Three very small RCTs in poor ovarian reserve patients reported conflicting results on the number of oocytes retrieved (Kansal Kalra et al., 2008, Kucuk et al., 2008, Rombauts et al., 1998). A very small RCT (18 women) reported no difference in number of oocytes retrieved (5.0 (3-8) vs. 5.5 (1-14)) between gonadotropin pre-treatment and normal-start stimulation in GnRH antagonist protocol (Kansal Kalra et al., 2008). Another very small RCT (40 women) reported similar findings in the short GnRH agonist protocol, with median number of oocytes collected: 4.5 (2-12) in the experimental group vs. 6 (1-10) in the control group (Rombauts et al., 1998). However, another very small RCT (42 women) reported an increased number of mature oocytes (mean number: 6.8 vs. 3.2) with luteal gonadotropin pre-treatment as compared to the normal-start stimulation in the long GnRH agonist protocol (Kucuk et al., 2008).

Luteal phase stimulation without fresh transfer

A small RCT compared luteal phase stimulation (n=31) with follicular phase stimulation (n=33) in women with a poor ovarian response to stimulation (Dastjerdi et al., 2024). Significantly more MII oocytes were retrieved with luteal stimulation (3 (0-8)) compared to follicular stimulation (2 (0-5)). Eleven women in both groups proceeded with embryo transfer resulting in 1 clinical pregnancy in the study group and none in the control group.

Another RCT investigated the effect of luteal phase stimulation in women with a poor ovarian response to stimulation (Suñol et al., 2023). In the ITT analysis, the mean number of MII oocytes retrieved was not different between the FPS and LPS groups (5.4±3.6 vs. 5.2±2.8).

Follicular versus luteal phase stimulation in double ovarian stimulation

An RCT compared double stimulation in one menstrual cycle (n=23) with one conventional ovarian stimulation cycle (n=23) (Boudry et al., 2024). The mean number of MII oocytes retrieved after follicular stimulation was 3.0±2.2 compared to 2.4±2.2 after luteal stimulation. However, the cancellation rate due to insufficient response for the second oocyte retrieval was 39.1% (9/23).

An RCT compared double stimulation in one menstrual cycle (n=21) with one conventional ovarian stimulation cycle (n=21) (Saharkhiz et al., 2024). The mean number of MII oocytes retrieved after follicular stimulation was 1.63 ± 1.40 compared to 1.72 ± 1.72 after luteal stimulation.

An RCT compared double stimulation (n=44) with 2 conventional ovarian stimulation cycles (n=44) using a GnRH antagonist protocol in women experiencing a poor ovarian response to stimulation (Massin et al., 2023). There was no significant difference in the mean number of MII oocytes retrieved after follicular and luteal stimulation (2.4±2.3 vs. 2.2±1.7). The cumulative cycle cancellation rate was similar in both groups 7.7% vs. 4.9%.

An RCT investigated the efficacy of double stimulation (n=28) in PGT-A cycles, compared to two conventional stimulation cycles (n=28) in women with a poor prognosis (Cerrillo et al., 2023). There was no significant difference in the mean number of MII oocytes retrieved after follicular and luteal stimulation (3.3±1.0 vs. 3.6±1.2).

Recommendations

Luteal start ovarian stimulation could be used when a fresh transfer is not intended and there is no possibility of natural conception. [updated]	Conditional ⊕◯◯◯

Late luteal phase start of gonadotropins with fresh transfer is probably not recommended for low responders. [updated]	Conditional ⊕◯◯◯

Justification

Mention should be made about late luteal gonadotropin start protocol (before menstruation), that can also be considered as gonadotropin pre-treatment. It has been used with intention of fresh transfer. Results are inconclusive and based on very little studies with very small study populations.

The quality of evidence is very low and controversial regarding the luteal start of FSH in normal and low responders, and there are no data for PCOS patients. However, the oocyte competence is probably not impacted by its luteal phase origin compared to follicular phase. Absence of adverse effects on neonatal outcomes and long-term child health needs to be evaluated on a larger scale.

A potential disadvantage of the luteal start stimulation is the mandatory freeze-all of oocytes or embryos. One study reported on neonatal outcomes comparing frozen/thawed from follicular and luteal phase stimulation (Chen et al., 2015). Therefore, luteal phase stimulation could be considered as an option in specifics cases, for organization and shortened time to oocyte retrieval, for example in urgent oncologic fertility preservation, as well as in freeze-all policy programs.

Also, the drug marketing approval for gonadotropin use in luteal phase needs to be considered.

DOUBLE STIMULATION

Double stimulation or “dual stimulation” or “duostim” (Vaiarelli et al., 2018) or “Shanghai protocol” (Kuang et al., 2014) is experimented in low responder patients or in urgent oncologic fertility preservation. It corresponds to the sequencing of 2 stimulation protocols within the same menstrual cycle: first in the follicular phase then second, immediately after the oocyte pick up, in the luteal phase of the same cycle. So, two oocyte pick-ups are performed at approximately 2 weeks apart. This protocol uses the physiological principles of multiple waves of folliculogenesis within one cycle (Baerwald et al., 2003). It allows to recover more oocytes in a shorter time period. As shown in luteal phase stimulation protocols, the quality of oocytes retrieved in the second stimulation seems as good as the ones retrieved in the first stimulation (same euploid embryo rate) (Vaiarelli et al., 2018).

Evidence

An RCT compared double stimulation in one menstrual cycle (n=44) with 2 conventional ovarian stimulation cycles (n=44) using a GnRH antagonist protocol in women experiencing a poor ovarian response to stimulation (Massin et al., 2023). No significant difference between double stimulation and

2 conventional stimulations for cumulative live birth rate (17.9% (7/39) vs. 34.1% (14/41)) or number of MII oocytes (2.4±2.3 vs. 2.5±2.7) was observed. No serious adverse events were reported.

Another RCT investigated the efficacy of double stimulation (n=28) in PGT-A cycles, compared to two conventional stimulation cycles (n=28) in women with a poor prognosis (Cerrillo et al., 2023). No significant differences were found with double stimulation or two conventional stimulations for live birth rate (19.5% (8/41) vs. 23.1% (9/39)), pregnancy rate (24.4% (10/41) vs. 23.1% (9/39)) or MII oocytes (6.8±1.7 vs. 8.7±1.8). The study was ended prematurely because of a high probability that no statistical differences would be confirmed at the end of study.

Recommendation

Double stimulation can be considered for urgent fertility preservation cycles. [2019]	GPP	

Double stimulation can be used with the intention to accumulate oocytes or embryos when fresh transfer is not planned. [updated]	Strong	⊕⊕◯◯

Justification

Two RCTs show that there is no benefit of double stimulation over two conventional stimulation cycles. There is a chance of pregnancy after the first ovarian stimulation as shown by the RCT by Boudry *et al.* (Boudry et al., 2024). In double stimulation, this would lead to an unnecessary second ovarian stimulation cycle.

A recent RCT investigated the start of the duostim cycle in the luteal phase in young low prognosis coupes (Racca et al., 2024). The second stimulation in the subsequent follicular phase can allow fresh transfer. No significant improvement in ongoing pregnancies were found compared to one standard follicular phase stimulation. Whether the surplus of cryopreserved blastocysts in the duostim group will provide benefits, compared to a second stimulation cycle with fresh transfer in the control group is the subject of further study.

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PART D: Fertility preservation and oocyte donation

10. Ovarian stimulation for fertility preservation

PICO QUESTION: WHAT IS THE PREFERRED STIMULATION PROTOCOL FOR FERTILITY PRESERVATION IN PATIENTS FACING GONADOTOXIC TREATMENT?

Fertility preservation represents a major issue for young women suffering from diseases that might impact their reproductive potential (Recommendations ASCO, ISFP). OS followed by oocyte or embryo vitrification constitutes the best option. Collecting as much oocytes as possible, sometimes in an extremely reduced time frame represents an important issue. Fertility preservation has emerged relatively recently in the field of reproductive medicine. Therefore, many questions raised, in particular regarding the preferred protocol and the feasibility of random-start ovarian stimulation. In addition, the specificity of OS performed in contexts of oestrogen-sensitive diseases has led, in the name of the precautionary principle, to the development of protocols using anti-oestrogen therapies. Considering the motivation for this treatment, critical and important outcomes in this chapter are different from the rest of this guideline. Critical outcomes for fertility preservation in this guideline are the number of oocytes/embryo's and preventing OHSS and other complications.

More information and recommendations on female fertility preservation for women with cancer, benign diseases, and also transgender patients and women undergoing elective freezing, is covered in the ESHRE guideline on female fertility preservation (www.eshre.eu/FFPguideline).

INITIATION OF STIMULATION

Evidence

Random-start

A systematic review and meta-analysis[21], including 2 prospective observational and 9 retrospective studies, compared random (688 cycles) and conventional start (1076 cycles) protocols for ovarian stimulation in cancer patients seeking fertility preservation (Sönmezer et al., 2023). No significant difference was found between random and conventional start of stimulation for number of MII oocytes retrieved (SMD -0.11, 95% CI -0.44 to 0.21, 6 studies, 787 cycles) and number of embryos frozen (SMD -0.04, 95% CI -0.28 to 0.20, 5 studies, 673 cycles).

In a prospective cohort study, ovarian stimulation was started irrespective of the menstrual cycle (early follicular, n=43; late follicular, n=17; or luteal, n=35) (Dezellus et al., 2024). The number of MII oocytes cryopreserved was not statistically different irrespective of the menstrual cycle phase (early follicular

[21] The cohort study by Muteshi *et al.*, 2018 is included in the new meta-analysis and therefore no longer mentioned separately.

10.0±7.3 vs. late follicular 7.7±4.0 vs. luteal 10.4±5.3). Seven embryo transfers with frozen-thawed oocytes were performed among five patients, none resulted in pregnancy.

In a retrospective cohort study, conventional start stimulation in the early follicular phase (n=176) was compared with the late follicular phase (n=8) start of ovarian stimulation for fertility preservation (Baig et al., 2023). No significant difference was found comparing early with late follicular phase start of stimulation for number of MII oocytes retrieved (9.0 (6.0-13.0) vs. (7.0 (2.3-13.3)).

In a retrospective cohort study, the cycle characteristics and outcomes of random-start ovarian stimulation (n=39) protocols were compared to the outcomes of conventional-start ovarian stimulation (n=117) cycles for women with breast cancer undergoing fertility preservation (Turan et al., 2023). The mean number of MII oocytes retrieved (10.9±4.2 vs. 10.1±5.8) and number of embryo's cryopreserved (77±4.0 vs. 7.7±4.8) was similar with random-start and conventional start stimulation. To date, seven women returned to utilize their cryopreserved embryos after RSCOS. Of those, six were conceived after the first single embryo transfer.

In a retrospective cohort study, random-start (n=36) was compared to conventional follicular start (n=25) in breast cancer patients undergoing ovarian stimulation for fertility preservation (Sahin et al., 2022). All patients received letrozole during ovarian stimulation independent of oestrogen receptor status. Random or follicular start of the ovarian stimulation did not significantly influence the total number of oocytes retrieved (10.9±6.9 vs. 11.5±9.3) or the number of MII oocytes retrieved (8.5±5.7 vs. 7.0±5.6).

Luteal start

A systematic review of 8 (non-randomized) studies of which 6 were performed in context of fertility preservation, showed in 251 women, that number of oocytes recovered (WMD −0.6 oocytes, 95 % CI −2.8 to 1.6) did not differ whatever the phase of the cycle at which FSH was started. Interestingly, oocytes obtained in cycles initiated in the luteal phase fertilized more efficiently (WMD 0.16, 95 % CI 0.13 to 0.19). No conclusion can be drawn on pregnancy and live birth rates regarding the very small number of patients and the extremely low re-utilization rates of cryopreserved oocytes and embryo in cancer patients (Boots et al., 2016).

In a retrospective cohort study, conventional start stimulation in the early follicular phase (n=176) was compared with the luteal phase start (n=52) of ovarian stimulation for fertility preservation (Baig et al., 2023). No significant difference was found comparing early follicular with luteal phase start of stimulation for number of MII oocytes retrieved (9.0 (6.0-13.0) vs. 11.5 (7.0-16.0)).

In a retrospective cohort study, conventional follicular ovarian stimulation (n=80) was compared to luteal phase ovarian stimulation (n=20) in women requiring gonadotoxic treatment (Jochum et al., 2019). Significantly more MII oocytes were retrieved after luteal phase ovarian stimulation compared to follicular phase (13.1±8.0 vs. 9.2±5.8).

In a prospective cohort study, the effectiveness of controlled ovarian stimulation in the follicular (n=68) and luteal phase (n=72) of the menstrual cycle in cancer patients for the preservation of reproductive material before gonadotoxic therapy was evaluated (Nazarenko et al., 2021). No significant difference was reported in the total number of oocytes retrieved (715 vs. 766) or the proportion of MII oocytes (520 (72.8%) vs. 557 (72.6%)).

Duostim or dual stimulation

A systematic review and meta-analysis including cohort studies compared the outcomes of single or double ovarian stimulation cycles for fertility preservation (Chen et al., 2022). As expected, a double ovarian stimulation significantly increased the total number of retrieved oocytes available for fertility preservation in comparison to one cycle (MD 7.91, 95% CI 3.42 to 12.40).

In a case series, the effectiveness of duostim was evaluated in 36 female oncology patients for fertility preservation (Puthur et al., 2023). A total of 324 oocytes were retrieved in the follicular phase stimulation, of which 184 were MII oocytes. A total of 337 oocytes were obtained after the luteal phase stimulation, of which 184 were MII oocytes. None of the thirty-six patients reported any symptoms of OHSS or delays to any previously planned cancer therapy.

In a retrospective cohort study, the optimal timing of second ovarian stimulation using the dual stimulation method in 69 good ovarian responders with cancer undergoing oocyte retrieval for fertility preservation was evaluated (Takeuchi et al., 2023). In the first (follicular) stimulation, the numbers of retrieved and matured oocytes were 7.5±5.6 and 5.3±3.9, respectively; in the second stimulation, these numbers were significantly higher (9.9±6.6 and 9.4±6.1, respectively). Based on their data, they advise an 8-day waiting interval for a stable retrieval in the second cycle for cases where >5 oocytes were retrieved in the first oocyte retrieval because of ovarian enlargement resulting in a poor response to stimulation and delayed follicular development.

Recommendation

For patients facing gonadotoxic treatment, ovarian stimulation for fertility preservation should be started irrespective of the menstrual cycle phase. [Updated]	Strong	⊕◯◯◯

Justification

For fertility preservation for patients facing gonadotoxic treatment, ovarian stimulation should be started as soon as possible, also in view of double stimulation. Solid evidence for the optimal waiting time in between ovarian stimulation cycles is currently lacking.

The systematic review and meta-analysis by Chen *et al.* shows that despite longer duration of stimulation and higher total gonadotropin consumption, the random-start stimulation finally led to similar number of oocytes retrieved, and metaphase II oocyte yield when compared with conventional start protocol. Therefore, random-start seems to be a viable strategy in the setting of fertility preservation for cancer patients, although additional pregnancy rate data are needed. These findings, however, should be interpreted with caution given the limitations of the analysis. These include lack of randomized controlled trials, small sample sizes, retrospective nature of most studies, lack of detailed information on gonadotropin and trigger types and heterogeneity among the studies included.

Current evidence indicates that oocyte competence is probably not impacted by its luteal phase origin compared to follicular phase. Absence of adverse effects on neonatal outcomes and long-term child health need to be evaluated on a larger scale, especially in cancer patients.

The drug marketing approval for gonadotropin use in luteal phase needs to be considered.

PITUITARY SUPPRESSION PROTOCOL

PITUITARY SUPPRESSION

Evidence

Only one retrospective analysis, including 24 women, compared the long GnRH agonist and GnRH antagonist protocols in women with breast cancer who were treated with FSH plus letrozole (Ben-Haroush et al., 2011). The number oocytes recovered was higher with GnRH agonist protocol (24.8±24.6 vs. 12.0±8.8), however this difference was not statistically significant. Furthermore, one patient had 82 oocytes retrieved after long GnRH agonist protocol. When this patient is excluded, the mean number of oocytes was 9.6 oocytes (range 0–30) (Ben-Haroush et al., 2011).

Two systematic reviews including a total of 33 studies (Boots et al., 2016; Rodgers et al., 2017) and 14 other investigations (Alvarez and Ramanathan, 2016, Cardozo et al., 2015, Chan et al., 2015, Das et al., 2011, Devesa et al., 2014, Druckenmiller et al., 2016, Garcia-Velasco et al., 2013, Johnson et al., 2013, Lawrenz et al., 2010, Lee et al., 2010, Muteshi et al., 2018, Pereira et al., 2016, Shapira et al., 2015) reported data of cancer patients having undergone ovarian stimulation for oocyte and/or embryo cryopreservation. More than 2200 cycles were described, most of them (>90%) with GnRH antagonist protocols. Among them, random-start ovarian stimulation or protocols using aromatase inhibitors or tamoxifen were considered. In addition, different methods of final oocyte maturation were used. The main outcome measure was usually the overall number of oocytes recovered and the number of mature oocytes obtained.

In a retrospective cohort study, ovarian stimulation with progestins for pituitary suppression combined with hMG and double trigger (n=46) was compared to pituitary suppression with a GnRH antagonist protocol combined with r-hFSH and trigger with hCG or GnRH agonist alone (n=78) (Filippi et al., 2023). Significantly more oocytes were retrieved with the GnRH antagonist protocol compared to the progestins (16 (10-21) vs. 10 (5-17)), however, the number of MII oocytes frozen was similar in both groups (10 (6-18) vs. 9 (4-14)). The number of cancelled cycles was also similar in both groups (3 (7%) vs. 5 (6%)).

In a retrospective cohort study, ovarian stimulation with progestins for pituitary suppression (n=20) was compared to GnRH antagonist (n=20) in patients with breast cancer for fertility preservation (Oliveira et al., 2021). No significant difference was noted comparing the GnRH antagonist protocol with progestins for the number of oocytes retrieved (4.5 (3-10.7) vs. 9 (4.1-12.8) or the proportion of MII oocytes (4 (2.1-9.8) vs. 7.5 (3.1-10)). There were 2 cases of OHSS in the GnRH antagonist group and 5 in the progestins group.

OVARIAN STIMULATION

Evidence

Fertility preservation in breast cancer represents a complex issue since this disease is considered as oestrogen sensitive. Indeed, ovarian stimulation for the purpose of freezing oocytes or embryos is associated with supra-physiological serum oestradiol levels that could theoretically result in the proliferation of malignant cells.

Therefore, innovative stimulation protocols have been developed in an effort to reduce potential harm associated with high oestradiol levels. Co-administration of either aromatase inhibitors or selective oestrogen receptor modulators during ovarian stimulation is used frequently.

A systematic review and meta-analysis[22], including 16 cohort studies, compared the outcomes of coadministration of aromatase inhibitors or tamoxifen cycles during ovarian stimulation for fertility preservation (Chen et al., 2022). No significant differences in the numbers of retrieved oocytes were observed between those using and not using letrozole regardless of ovarian stimulation protocol (mean difference −0.55; 95% CI −2.01 to 0.91) and similar results were observed with the used of tamoxifen (mean difference 0.67; 95% CI −1.29 to 2.64). A significantly lower peak serum oestradiol concentration was observed in letrozole-based groups than in letrozole-free groups (mean difference −1.22; 95% CI −1.42 to −1.02).

A systematic review and meta-analysis investigated the effect of tamoxifen supplementation compared to letrozole for patients with oestrogen-sensitive breast cancer undergoing ovarian stimulation for fertility preservation (Yoshida et al., 2023). No significant difference was reported for the number of oocytes retrieved (MD -0.47, 95% CI -3.84 to 2.90, 2 RCT) or MII oocytes (MD 0.22, 95% CI -2.20 to 2.64, 2 RCT).

In a retrospective cohort study, the outcomes of women with oestrogen-sensitive breast cancer undergoing ovarian stimulation with tamoxifen supplementation (n=154) were compared to women with non-oestrogen-sensitive breast cancer having ovarian stimulation without tamoxifen (n=60) (Sii et al., 2023). No significant difference was noted between ovarian stimulation with or without tamoxifen for the total number of oocytes retrieved (13.8 (12.1-15.4) vs. 12.0 (9.7-14.3)) or number of MII oocytes retrieved (10.5 (9.1-12.0) vs. (8.9 (7.3-10.5)).

In a retrospective cohort study, the impact of letrozole use in oocyte cryopreservation (n=48, 55 cycles) among adolescent and young adult cancer patients for fertility preservation was investigated and compared to conventional gonadotropin stimulation (n=25, 26 cycles) (Suzuki et al., 2023). There was no significant difference between ovarian stimulation with or without letrozole for the total number of oocytes retrieved (10.4±6.4 vs. 9.3±5.7) or their maturation rate (69.6±25.8% vs. 68.6±25.8%).

A retrospective cohort study included women undergoing ovarian stimulation for fertility preservation with the GnRH antagonist protocol, with (n=84) or without the use of supplemental letrozole (n=162) (Lalami et al., 2022). There was no significant difference in the number of oocytes retrieved (14.2±0.7 vs. 14.0±0.8) nor number of embryos cryopreserved (7.0±4.3 vs. 4.2±2.9) with or without letrozole supplementation during ovarian stimulation.

In a retrospective cohort study, the effects of letrozole (n=36) or tamoxifen (n=30) coadministration on the outcomes of ovarian stimulation for fertility preservation were assessed and compared to conventional gonadotropin stimulation (n=52) (Shulman et al., 2021). There was no significant difference in number of oocytes retrieved or maturation rate with letrozole or tamoxifen coadministration compared to conventional stimulation (12 (7.5-18.5) and 78.6% MII vs. 12 (8-20.3)

[22] The meta-analysis by Rodgers *et al*., 2017 cited here in the 2018 version of the guideline was replaced by a more recent meta-analysis. The retrospective cohort study by Pereira *et al*., 2017 is included in the new meta-analysis and therefore no longer mentioned separately.

and 79% MII vs. (10.5±6-18) and 81.5% MII). The number of cryopreserved embryo's was also similar between groups (7 (2-10) vs. 5 (3-12.5) vs. 5 (3-7.5)).

In a retrospective cohort study, the effect of letrozole supplementation (n=94) during ovarian stimulation for fertility preservation was compared to conventional gonadotropin stimulation (n=83) (Sonigo et al., 2019). There was no significant difference noted for the number of oocytes retrieved with or without letrozole supplementation (12.2±8.3 vs. 13.1±10.0), however, the maturation rate was significantly lower with letrozole supplementation during ovarian stimulation (64.9±22.8% vs. 77.4±19.3%).

Recommendation

For ovarian stimulation in women seeking fertility preservation for medical reasons the GnRH antagonist protocol is recommended. [2019]	Strong ⊕◯◯◯

In ovarian stimulation for fertility preservation in oestrogen sensitive diseases the concomitant use of anti-oestrogen therapy, such as letrozole or tamoxifen, can be considered. [2019]	GPP

Justification

There is low-quality evidence of the necessity of considering a specific GnRH analogue protocol. GnRH antagonist protocols are preferred since they shorten the duration of OS, offer the possibility of triggering final oocyte maturation with GnRH agonist in case of high ovarian response, and reduce the risk of OHSS. Moreover, especially in cancer patients, who are at higher risk of thrombosis due to their oncologic status, GnRH antagonist protocols seem to be preferred since they enable GnRH agonist trigger, therefore reducing the risk of OHSS. Melo et al. reported that 3.1% of study participants had a thromboembolic event at a median of 0.25 years from oocyte aspiration for fertility preservation and 0.33 year from their cancer diagnosis (Melo et al., 2022). PPOS is a newer strategy for pituitary suppression and early evidence suggests its use can be considered in oncologic patients as well. However, safety data are lacking for patients with progesterone receptor positive breast cancer.

RCTs aiming to compare GnRH agonist and GnRH antagonist protocols for fertility preservation may be interesting. However, considering such studies may be difficult since GnRH agonist trigger represents an important advantage in this field.

Data on live births are dramatically lacking, in particular in cancer patients having vitrified oocytes.

Current evidence indicates that in ovarian stimulation for fertility preservation in oestrogen sensitive diseases the concomitant use of anti-oestrogen therapy, such as letrozole or tamoxifen, can be considered to reduce oestrogen levels. As discussed in chapter 6 on gonadotropins, the use of anti-oestrogen therapy is probably not recommended for the purpose of improving the outcome. The quality of evidence is still low given the number and quality of studies available. The existing literature

concerning ovarian stimulation for fertility preservation in women with oestrogen sensitive cancer is limited by its observational nature, small patient numbers and relatively short duration of follow-up. Definitive statements regarding the safety of OS in women with a recent diagnosis of breast cancer would require long-term and large-scale studies, and these do not yet exist. A recent retrospective cohort study reported that the 5-year invasive disease-free survival was not statistically different between the fertility preservation recipients and a subgroup of patients cotreated with tamoxifen during stimulation because of oestrogen-receptor positive disease (HR 1.66, 95% CI 0.67-3.49) (Shapira et al., 2025).

Undertaking RCTs in this patient population represents a major limitation. It is not known whether the transient period of raised oestrogen concentrations during ovarian stimulation is harmful to women with breast cancer. A study aiming to compare the short- and long-term effects of ovarian stimulation with or without letrozole co-administration is ongoing. However, the use of letrozole is off-label for OS and safety concerns have been raised regarding possible teratogenicity associated with letrozole.

Aromatase inhibitors protocols enable GnRH agonist trigger (Oktay et al., 2010, Reddy et al., 2014).

FINAL OOCYTE MATURATION PROTOCOL

Evidence

In a retrospective cohort study, patients undergoing ovarian stimulation for fertility preservation received depot GnRH agonist (n=22), short-acting GnRH agonist (n=26) or hCG (10.000 IU; n=34) for final oocyte maturation (Massarotti et al., 2023). There was no significant difference between long-acting, short-acting or hCG triggering for the number of oocytes retrieved or MII rate (13.9±5.2 (80% mature) vs. 18±10.3 (80% mature) vs. 11.5±6.7 (74% mature)). No cases of OHSS were reported after the long-acting GnRH agonist trigger, and 1 case after the short-acting GnRH agonist trigger and the hCG trigger.

In a retrospective cohort study, 293 patients (373 cycles) underwent ovarian stimulation for fertility preservation with the GnRH antagonist protocol. Final oocyte maturation was triggered with double trigger (n=148) in the study group compared to rhCG triggering in the control group (n=225) (Hong et al., 2022). No significant difference was found when comparing rhCG to double triggering for the number of oocytes retrieved (7.9±5.7 vs. 8.8±7.2), the proportion of MII oocytes (4.8±3.8 vs. 5.7±4.9) or the number of OHSS cases (5/225 (2.2%) vs. 7/148 (4.7%)).

Recommendation

For final oocyte maturation in patients facing gonadotoxic treatment, GnRH agonist is preferred. [2025]	GPP

Justification

Final oocyte maturation is a key step for fertility preservation. hCG has been the conventional strategy to induce final oocyte trigger. However, GnRH agonist trigger in antagonist protocols represents a safe option to limit the risk of ovarian hyperstimulation syndrome. Current evidence regarding the best trigger option is of low-quality, only based on retrospective studies. Therefore, hCG still appear to be

the preferred strategy for inducing final oocyte maturation in case of normal ovarian response to stimulation.

PICO Question: What is the preferred stimulation protocol for elective oocyte cryopreservation?

Initiation of stimulation

Evidence

In a prospective cohort study, patients presenting for elective oocyte preservation were offered the choice for either random-start (n=443) or conventional day 2/3 start (n=859) stimulation (Pereira et al., 2017). No significant difference was observed for number of MII oocytes retrieved with either random-start (early follicular, late follicular or luteal start) or conventional day 2/3 start stimulation (10.8±2.7 vs. 11.1±3.0 vs. 10.9±3.2 vs. 13.1±2.3).

Recommendation

Ovarian stimulation for elective oocyte preservation can be started irrespective of the menstrual cycle phase. [2025]	Conditional ⊕◯◯◯

Justification

Since in elective oocyte freezing cycles all oocytes will be cryopreserved, ovarian stimulation can be started irrespective of the menstrual cycle phase.

Pituitary suppression protocol

Pituitary suppression

Evidence

In a retrospective cohort study, including women of advanced maternal age undergoing elective oocyte cryopreservation, the use of a progestin protocol (n=89) was compared to a GnRH antagonist protocol (n=178) (Vaiarelli et al., 2024). No significant difference in the number of MII oocytes retrieved was reported between the progestin and GnRH antagonist protocol (6.8±5.6 vs. 6.2±4.1). A total of 61 and 107 vitrified-warmed euploid SETs were performed. No significant difference was observed for cumulative LBR (24.7% (21/85) vs. 21.9% (39/178)) or live birth rate/transfer ((37.7% (23/61) vs. (39.3% (42/107)) between progestin and GnRH antagonist protocol.

Ovarian stimulation

Evidence

In a retrospective cohort study, 217 patients presenting for elective oocyte cryopreservation underwent a first IVF cycle with 300 IU r-hFSH and a second IVF cycle with an adjusted r-hFSH dosage

(increased, decreased or no change) (Orvieto et al., 2022). Comparing the first to the second ovarian stimulation cycle, significantly more MII oocytes were retrieved in the second cycle (8.96±5.19 vs. 8.04±4.7). In the second ovarian stimulation cycle, 23 (10.6%) women received a lower daily gonadotropin dose, 60 (27.6%) received the same dose and 134 (61.7%) an increased daily dose. Those who achieved a lower oocyte yield in the second cycle received significantly higher daily dose of gonadotropins (415±88 IU vs. 369+106 IU).

Recommendation

GnRH antagonist or progestin protocol are probably recommended over GnRH agonist protocols for pituitary suppression in elective oocyte cryopreservation.	Conditional ⊕◯◯◯

Justification

Only low-quality evidence from one retrospective cohort study was available in the elective oocyte cryopreservation population. However, data from the general infertility population showed that GnRH antagonist and progestin protocol are preferred over GnRH agonist protocol for elective cryopreservation. The reader is referred to chapter 6 for information on the choice of gonadotropins for ovarian stimulation for elective oocyte cryopreservation.

FINAL OOCYTE MATURATION PROTOCOL

Evidence

In a retrospective cohort study, reproductive outcomes were compared after GnRH agonist (n=40) or hCG (n=29) for the final oocyte maturation trigger (Herzberger et al., 2021). The decision was made according to laboratory and sonographic results on the day of triggering, with the risk of OHSS considered. Patients included in the GnRH agonist trigger group were significantly younger compared to the hCG group. Significantly more oocytes were retrieved after GnRH agonist trigger compared to hCG (16.5 (8.0-25.0) vs. 6.0 (2.5-11.0). However, the maturation rate was comparable (0.8 (0.7-0.9 vs. 0.8 (0.7-1.0)).

In a retrospective cohort study, it was examined whether GnRH agonist trigger (n=959) for final oocyte maturation can be reliably used and was compared to hCG (n=671) and dual trigger (n=50) (Maslow et al., 2020). Cycles using hCG trigger were characterised by significantly higher age and lower AMH and LH. Significantly less MII oocytes were retrieved with hCG trigger compared to GnRH agonist and dual trigger (8.4±5.9 vs. 13.3±9.1 vs. 13.0±7.8). There were no cases of severe OHSS requiring hospitalisation, medical or surgical intervention.

In a retrospective cohort study, dual trigger (n=40) was compared to hCG trigger (n=36) for final oocyte maturation in patients with diminished ovarian reserve undergoing elective cryopreservation (Kim et al., 2020). Significantly more MII oocytes were retrieved with dual trigger compared to hCG trigger (3.7±2.7 vs. 2.3±1.7). Furthermore, the oocyte maturation rate was significantly higher after dual trigger compared to hCG trigger (68.5% (146/213) vs. 45.6% (82/180)).

Recommendation

For final oocyte maturation in elective oocyte cryopreservation, GnRH agonist is preferred. [2025]	GPP

Justification

hCG and GnRH agonist for final oocyte maturation result in similar numbers of mature oocytes. However, if GnRH agonist is used for final oocyte maturation, the risk of OHSS is significantly reduced.

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11. Ovarian stimulation for oocyte donation

PICO Question: What is the preferred stimulation protocol for oocyte donation?

Considering the motivation for ovarian stimulation for oocyte donation, critical and important outcomes in this chapter are different from the rest of this guideline. Critical outcomes for ovarian stimulation for oocyte donation in this guideline are the number of oocytes/embryo's and preventing OHSS and other complications.

Initiation of stimulation

Ovarian stimulation in the luteal phase, several case reports have described spontaneous pregnancies that were undetectable at the time of starting ovarian stimulation. This carries the risk of early pregnancy exposure to medications used during ovarian stimulation, as well as the risk of ovarian hyperstimulation syndrome due to endogenous hCG production. It is therefore essential to inform oocyte donors about the risk of natural conception prior to commencing random-start ovarian stimulation (Lawrenz et al., 2024, Semrl et al., 2024).

Evidence

In an RCT, 67 oocyte donors were randomised to receive ovarian stimulation starting either in the early (n=35) or late (n=32) follicular phase in a GnRH antagonist protocol (De Rijdt et al., 2024). There was no significant difference in the number of MII oocytes retrieved when comparing early to late follicular stimulation (14.1±8.1 vs. 12.7±8.5). No cases of OHSS were reported in either group.

In a prospective cohort study, oocyte donors underwent two consecutive ovarian stimulation protocols with at least one month in between both cycles. The cycles were identical, aside from the start of stimulation, follicular phase in the first cycle and luteal phase in the second cycle (Martinez et al., 2022). There was no significant difference for number of MII oocytes with follicular or luteal start stimulation (20.27±9.60 vs. 20.73±8.65). The mean number of euploid embryos was equivalent between the follicular and the luteal start groups (1.59±1.30 vs. 1.61±1.17). At the time of publication, 42 recipients have undergone at least one FET, with a total of 68 FET being performed. Clinical pregnancy rate was 42.9% for the follicular phase stimulation and 59.0% for the luteal phase stimulation.

In a retrospective cohort study, live birth rates were investigated in recipients matched with donors using random-start or conventional follicular start ovarian stimulation (Guerrero et al., 2024). There were no significant differences in the total number of oocytes retrieved (17.2±8.5 vs. 17.6±8.8) or MII oocytes retrieved (13.5±7.0 vs. 13.8±7.1) between random and conventional start ovarian stimulation. There was no significant difference in live birth rate in recipients with oocytes retrieved after random start or conventional start ovarian stimulation (46.6% (201/537) vs. 47.7% (62/173); OR 0.88, 95% CI 0.48-1.58).

Recommendation

Conventional follicular start or random-start ovarian stimulation are equally recommended for oocyte donation cycles. [2025]	Strong	⊕○○○

If random-start ovarian stimulation is used, oocyte donors need to adopt contraceptive measures to prevent the possibility of a natural pregnancy. [2025]	GPP

Justification

Current evidence in oocyte donors reports no difference in efficacy in terms of the number of oocytes or the number of mature oocytes retrieved, and no difference in the live birth rate in oocyte recipients when stimulation is initiated in the early follicular or luteal phase. This supports the option of random-start ovarian stimulation protocols for oocyte donors. Some studies have reported unexpected spontaneous pregnancies during ovarian stimulation with random-start protocols, the possibility of which must be carefully excluded before commencing ovarian stimulation.

PITUITARY SUPPRESSION PROTOCOL

CONTRACEPTIVE PRE-TREATMENT

Evidence

No randomised controlled studies were identified for this section.

In a retrospective study, including 491 consecutive cycles of vitrified oocyte donation undergoing ovarian stimulation using GnRH antagonist co-treatment and GnRH agonist trigger, the use of contraceptive pre-treatment with an IUD (n=103 cycles) was compared to no pre-treatment (n=388 cycles) (Galvão et al., 2019). Comparing contraceptive pre-treatment to no pre-treatment, no significant differences were found for the number of MII oocytes retrieved (14.5±6.9 vs. 14.2±7.3) and number of top quality embryos (2.3±1.2 vs. 2.3±1.3). Cumulative live birth rate per embryo transfer in oocyte recipients was also similar between groups (49% (47/96) vs. 45.3% (162/358).

In a prospective cohort study oocyte donors were assigned to receive ovarian stimulation after 5 days (n=42), or after 7 days of pill discontinuation (n=50) in a GnRH antagonist protocol (Pérez-Calvo et al., 2017). Extended pill-free interval of 7 days did not significantly influence the number of MII oocytes retrieved (12.4±7.4 vs. 10.6±4.9).

Recommendation

Any type of contraception (hormonal, non-hormonal, oral, vaginal or intrauterine) can be used before initiation of ovarian stimulation in oocyte donors.[2025]	GPP

Progestin or intrauterine contraception can be used during ovarian stimulation in oocyte donors.[2025]	GPP

Justification

Current evidence in oocyte donors reports no difference in efficacy in terms of the number of oocytes or the number of mature oocytes retrieved, when comparing pre-treatment with OCP or IUD to no pre-treatment. Furthermore, no differences were observed in the cumulative live birth rates in oocyte recipients. An extended pill free interval of 5 or 7 days is usually recommended prior to initiation of stimulation.

PITUITARY SUPPRESSION

Evidence

GnRH analogues

In a systematic review and meta-analysis, clinical outcomes were compared between the use of GnRH agonists and antagonists in oocyte-donation cycles (Bodri et al., 2011). Comparing GnRH agonist and GnRH antagonist protocols, no significant difference was found for the number of retrieved oocytes (WMD 0.60, 95% CI 2.26 to 1.07, 7 RCT, 932 donors). Although OHSS incidence was not different between treatment groups (RR 0.61, 95% CI 0.18-2.15, 4 RCT), results should be interpreted with caution, since this might be related to the small sample size, unable to detect any significant differences.

A prospective cohort study investigated the use of a long-acting GnRH antagonist in comparison to the use of a conventional GnRH antagonist in historic controls (Boniface et al., 2023). The average number of total oocytes retrieved was similar between the control and study group (30.55 vs. 30.31). The average number of mature oocytes was similar as well between the control and study group (25.42 vs. 24.73).

In a retrospective cohort study, the clinical outcomes were compared between clomiphene-citrate (n=133) and GnRH antagonist-based protocols (n=100) in donor cycles (Singh et al., 2016). The number of MII oocytes retrieved (13.04±5.73 vs. 12.96±6.08) and the number of grade I embryos (8.32±5.09 vs. 7.95±4.77) was similar in the clomiphene citrate and the GnRH antagonist groups. The number of OHSS cases was also similar between groups (10 vs. 9). No significant difference was reported in live birth rate per started cycle: 47.8% in the clomiphene group and 39.55% in the GnRH antagonist group.

Progestins

In a systematic review and meta-analysis, clinical outcomes were compared between the use of progestins and GnRH antagonist protocols for pituitary suppression in oocyte donors (Martinez et al., 2021). Meta-analysis of the 2 RCTs comparing PPOS with GnRH antagonist protocols for the treatment in 490 oocyte donors showed no differences in mean number of retrieved oocytes (MD 0.33, 95% CI -1.30 to 1.96) and in clinical pregnancy rate among 625 recipients (OR 0.83, 95% CI 0.33-2.06).

In an RCT, reproductive outcomes were compared in oocyte donors undergoing pituitary suppression with progestins (n=161) versus conventional treatment with a GnRH antagonist (n=157) (Giles et al., 2021). No significant difference was found between the study and control group for the number of MII oocytes retrieved (16.7±9 vs. 16.9±7.7). Cumulative live birth rate (70.6% (130/175) vs. 68.7% (121/171)) and live birth rate (52.7% (90/175) vs. 47.1% (83/171)) were not significantly different in recipients of the oocytes after the use of the progestin or GnRH antagonist protocol.

Recommendation

For pituitary suppression in oocyte donors the GnRH antagonist and progestin protocol are probably equally recommended. [2025]	Conditional ⊕⊕◯◯

A GnRH agonist protocol for pituitary suppression is not recommended in oocyte donors. [2025]	GPP

Justification

Although GnRH agonist and GnRH antagonist protocols in oocyte donors result in comparable numbers of oocytes and mature oocytes, and result in similar live birth, the use of GnRH agonists is associated with higher risk of OHSS. There is low-quality evidence that ovarian stimulation in oocyte donors using the GnRH antagonist protocol or progestin-primed ovarian stimulation yield similar numbers of oocytes and mature oocytes, and result in similar live birth and cumulative live birth rates in oocyte recipients. Both offer the possibility of triggering final oocyte maturation with a GnRH agonist, minimising the risk of OHSS and optimising safety for oocyte donors.

The use of a long-acting GnRH antagonist has been studied only in a cohort study design, without reporting the effects on the outcome live birth. The same is reported for the use of Clomiphene citrate and recommendations are therefore not given. Given the high risk of OHSS long-acting agonist should not be recommended in oocyte donors.

OVARIAN STIMULATION

Evidence

Type of stimulation drug

In an RCT, healthy oocyte donors were randomly assigned to start ovarian stimulation with a single dose of long-acting r-hFSH 7 days after OCP discontinuation (n=90), compared to a conventional protocol where ovarian stimulation is started 5 days after OCP discontinuation with a single dose of long-acting r-hFSH followed by additional 225 IU r-hFSH starting on day 8 (n=90) in the GnRH antagonist protocol (Alvarado Franco et al., 2023). The number of MII oocytes retrieved was significantly lower in the study group compared to the control group (10 (6-14) vs. 12 (9-17.25)).

In an RCT, three types of gonadotropins were compared in an oocyte donor programme: long-acting r-hFSH (n=68), r-hFSH (150 IU, n=69) and hMG (225 IU, n=71) (Cruz et al., 2017). Comparing long-acting r-hFSH to r-hFSH and hMG, no significant difference was observed for the number of MII oocytes retrieved (12.2±1.1 vs. 12.1±1.4 vs. 12.3±2.1) and cycle cancellation for poor response (2/68 vs. 2/69 vs. 5/71). Clinical pregnancy rates in oocyte recipients were similar: 60.5% for the long-acting r-hFSH group; 59.5% for the r-hFSH group; and 63.2% for the hMG group.

In an RCT, participants were randomly assigned to one of three gonadotropin regimens: r-hFSH only (n=346), hMG only (n=333) or r-hFSH and hMG combination (n=349) in a GnRH agonist protocol (Melo

et al., 2010). When comparing r-hFSH only to hMG only and the r-hFSH and hMG combination, there was no significant difference reported for risk of mild and moderate OHSS (7.04% (20/284) vs. 6.78% (19/280) vs. 5.52% (16/290)), number of top quality embryos (3.4±0.4 vs. 3.5±0.5 vs. 3.6±0.4) or cycle cancellation rate (18% (62/346) vs. 16% (53/333) vs. 17% (59/349)). No cases of severe OHSS were observed. No significant differences were observed in clinical pregnancy rates in oocyte recipients after r-hFSH (56.7% (199/351)), hMG (57% (207/363)) or r-hFSH and hMG combination (59.2% (216/365)) for ovarian stimulation.

In an RCT, oocyte donors were randomly assigned to received either r-hFSH alone (n=127) or r-hFSH with LH supplementation by hMG on stimulation days 5-7 (n=126) in a long GnRH agonist protocol. The groups were further stratified based on their baseline LH levels: baseline LH < 1 IU/L (groups 1 and 2, without and with supplemental LH activity, respectively) and baseline LH > 1 IU/L (groups 3 and 4, without and with supplemental LH activity respectively). On stimulation day 5, the groups were further stratified based on their oestradiol levels: <100 pg/ml (a) and ≥100 pg/ml (b) (Tesarik and Mendoza, 2002). The number of MII oocytes per donor was significantly higher in all groups co-stimulated with LH when compared with corresponding groups stimulated with FSH alone. In women with baseline LH < 1 IU/L, the number of good-quality cleavage-stage embryos was significantly higher with LH activity supplementation. No differences in pregnancy rates were detected between any comparable groups with and without the inclusion of exogenous LH to the stimulation protocol.

In an RCT, participants were randomly assigned to receive either hp-FSH (n=20) or hMG (n=21) for ovarian stimulation in an oocyte donation programme (Söderström-Anttila et al., 1996). One donor in each group developed moderate OHSS after oocyte retrieval. Two cycles were cancelled, one in each group. 53% of the donors in the hp-FSH group (10/19) and 42% in the hMG group (8/19) had complaints about side-effects and discomfort (headache, tiredness, abdominal swelling and pain, nausea and irritability). One donor in the hp-FSH group and two donors in the hMG group experienced a mild fever reaction.

In an RCT, ovarian stimulation with r-hFSH alone (225IU, n=20) was compared to r-hFSH (225 IU) combined with LH (75 IU) from day 6 of stimulation (n=22) in a short GnRH agonist protocol for oocyte donors (Acevedo et al., 2004). The number of MII oocytes retrieved (80 vs 71) and the number of grade I embryos (17 vs. 3) was significantly higher with LH supplementation compared to no supplementation. None of the donors developed severe OHSS. No significant difference was reported in clinical pregnancy rate (51% vs. 30%) in oocyte recipients.

Dosing and formulation

In a prospective cohort study, clinical outcomes were compared between two ovarian stimulation cycles in the same high responder oocyte donors: a dose of 225 IU (n=32) stimulation protocol, followed by a dose of 150 IU (n=32) stimulation protocol (Rubio et al., 2010). The number of MII oocytes retrieved was significantly lower with the lower dose compared to the higher dose (262 vs. 428). Only 22 donors completed both cycles, for 10 donors, the reduced-dose cycle was cancelled for low response. The number of live births was similar after 150 IU or 225 IU for ovarian stimulation (13 vs. 11).

In a retrospective cohort study, clinical outcomes were compared between r-hFSH filled by mass (n=12 cycles) compared to r-hFSH filled by conventional bioassay (n=11 cycles) in the same oocyte donors (Martinez et al., 2007).The number of oocytes retrieved was significantly higher with r-hFSH filled by

mass compared to r-hFSH filled by bioassay (23.8±8.7 vs. 17.1±8.5). The number of day-5 embryos was similar in both groups (5.4±3.1 vs. 5.1±3.0). There were no cases of OHSS reported in either group.

In a retrospective cohort study, clinical outcomes and patient satisfaction were compared between reconstituted r-hFSH (n=19 cycles) or a cartridge pen system (n=79 cycles) in oocyte donors (Christianson et al., 2007). The number of MII oocytes retrieved was not significantly different with the reconstituted r-hFSH or the pen system (23.7±3 vs. 23.1±1.3). Donors scored significantly higher medication tolerance scores using the cartridge pen device (3.9 ± 0.4 vs. 3.1 ± 0.6, $p < 0.05$). Five donors who had used both formulations also noted greater satisfaction using the cartridge pen device r-hFSH compared to reconstituted r-hFSH (3.7 ± 0.2 vs. 3.1 ± 0.4, $p < 0.01$,respectively). No significant difference was reported in clinical pregnancy rate per embryo transfer in oocyte recipients (45% (8/18) vs. 61% (55/90).

Recommendation

The use of recombinant human FSH (r-hFSH), purified FSH, long-acting r-hFSH or hMG is probably equally recommended in oocyte donors undergoing ovarian stimulation. [2025]	Conditional ⊕◯◯◯

Gonadotropin dose should be individualised based on ovarian reserve with the goal to maintain donors' safety and also obtain an optimal number of oocytes. [2025]	GPP

Justification

Several randomised, controlled trials have shown no difference in the number of oocytes or number of embryos obtained using different FSH preparations in oocyte donors. One RCT reported a high cycle cancellation rate due to low response in donors receiving 150 IU FSH/day compared to 225 IU FSH/day. No studies have reported on live birth outcomes, and further clinical research is required.

The issue of dosing in oocyte donation cannot be answered with the current evidence.

FINAL OOCYTE MATURATION PROTOCOL

Evidence

A Cochrane systematic review and meta-analysis, including three RCTs and 372 donors, compared hCG trigger with GnRH agonist for final oocyte maturation in oocyte donors (Youssef et al., 2014). The incidence of OHSS was lower with GnRH agonist compared to hCG for final oocyte maturation (OR 0.05, 95% CI 0.01-0.28, 3 RCT, 372 donors) and mild-moderate OHSS was observed only after hCG triggering. No significant difference was found for the number of retrieved oocytes between GnRH agonist and hCG for final oocyte maturation. Live birth rate was similar between hCG and GnRH agonist trigger (OR 0.92, 95% CI 0.53-1.61, 1 RCT, 212 women).

A meta-analysis found no differences in the CPR among the corresponding recipients after ovulation triggering with GnRH agonist or hCG (OR 0.86, 95% CI 0.58-1.26, 4 RCT, 460 donors) (Martinez et al., 2021).

An RCT compared two different recombinant hCG (r-hCG) doses, 250 µg (n=57) and 500 µg (n=55), for final oocyte maturation in a GnRH antagonist protocol in oocyte donors (Clua et al., 2012). Comparing the lower to the higher rhCG dose, no significant difference was noted in the number of MII oocytes retrieved (10.1±3.2 vs. 9.2±3.4). Mild OHSS was observed in 17 donors (29%) of the 250 rhCG dose group and in 23 (39%) of the 500 lg r-hCG dose group. Clinical pregnancy rate was similar in oocyte recipients (56.1% (32/57) vs. 58.2% (32/55)).

In a retrospective cohort study, clinical outcomes were compared after hCG (42 cycles), GnRH agonist (232 cycles) and dual (59 cycles) trigger for final oocyte maturation in oocyte donor cycles (Jones et al., 2021). The number of MII oocytes retrieved was significantly lower after hCG trigger compared to GnRH agonist and dual trigger (7.1±3.4 vs. 11.2±5.5 vs. 11±6.0). Significantly more cases of OHSS were reported after dual trigger compared to hCG and GnRH agonist trigger (8.5% (5/59) vs. 0% vs. 0.4% (1/232)).

Recommendation

The routine use of a GnRH agonist trigger is recommended in oocyte donors using the GnRH antagonist or progestin protocols for pituitary suppression. [2025]	Strong	⊕⊕◯◯

The use of a hCG trigger is not routinely recommended in oocyte donation cycles. [2025]	Strong	⊕⊕◯◯

Justification

Two systematic reviews and meta-analysis reported similar oocyte and mature oocyte yield between GnRH agonist triggering and hCG triggering, while no differences in the CPR among the corresponding recipients were observed. Owing to the risk of ovarian hyperstimulation syndrome when using an hCG trigger compared to a GnRH agonist trigger hCG trigger should not be recommended in oocyte donation cycles. The GDG has not considered the rare occasions where the donor has gonadotropin insufficiency. In most oocyte donors, GnRH agonist should be used for safety (OHSS). However, there may be cases where hCG is needed.

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PART E: Monitoring

12. Hormonal assessment during ovarian stimulation

PICO Question: When to start monitoring of follicular development?

Monitoring the response of the ovaries to the gonadotropin stimulation serves the purpose of knowing the number and size of follicles that is growing and are expected to deliver a useful oocyte after the follicle aspiration. In addition, the size and number of follicles with a certain diameter can be assessed in order to time the moment of the ovulation trigger. Although usual practice consists of a baseline ultrasound scan, with follow up ultrasound monitoring from day 8 of the stimulation onwards, quite some practice variation exists. The same is true for hormonal assessments that mainly focus on the degree of pituitary suppression, the development of early progesterone rises and the measurement of oestradiol as an indicator of follicle numbers. For none of these markers scientific studies exist to demonstrate a benefit of certain starting moments.

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

A survey was conducted to understand the global practice of routine hormone monitoring during ovarian stimulation for IVF/ICSI (Sachs-Guedj et al., 2023). Most respondents (98.9%) used ultrasound for monitoring ovarian stimulation cycles. Hormonal monitoring was widely accepted and used by 420 (79.5%) of participants during any of the cycle monitoring visits. Oestradiol was the most frequently monitored hormone during the first and second/third clinic visit after the first gonadotropin injection. Hormone monitoring was most commonly performed on the day of, or day prior to final oocyte maturation, with 71% of respondents measuring oestradiol. The number of respondents who measured P4 (67.7%) was twice that during the second/third visit. There was also an increase in the proportion of respondents measuring LH, from 27.3% in the second/third visit, to 31.5% in the visit on the day of, or day prior to ovulation triggering. Oestradiol monitoring was used by 74% of respondents for the prediction of ovarian hyperstimulation syndrome (OHSS). Among the respondents, 23.5% measured progesterone in all patients or nearly all patients, and 21.1% measured it in some patients. Most respondents (60.7%) believed that hormones play an important role in monitoring ovarian response during OS, and 56% considered that HA is important to guide decision-making for the prevention of OHSS.

Ultrasound and oestradiol measurements

Evidence

A Cochrane meta-analysis on monitoring of ovarian stimulation in IVF/ICSI with ultrasound alone compared to ultrasound plus serum oestradiol concentration combined 6 RCTs including 781 women (Kwan et al., 2014). Monitoring of the stimulation phase by using serum oestradiol measurements and ultrasound did not appear to decrease the probability of OHSS (6 RCT, OR 1.03, 95% CI 0.48-2.20, 781 women), nor increase the probability of clinical pregnancy (4 RCT, OR 1.10, 95% CI 0.79-1.54, 617

women), or the number of oocytes retrieved (5 RCT, WMD 0.32, 95% CI -0.60 to 1.24, 596 women) (Kwan et al., 2014).

Recommendation

The addition of oestradiol measurements to ultrasound monitoring is probably not recommended. [2019]	Conditional ⊕⊕◯◯

Justification

On the basis of the currently published evidence, monitoring of the stimulation phase by serum oestradiol measurements and ultrasound is not superior to monitoring by ultrasound alone in terms of efficacy and safety. The addition of oestradiol in the monitoring does not appear to increase the probability of pregnancy, the number of oocytes retrieved, or to decrease the probability of OHSS.

From the six studies included in the meta-analysis, a GnRH agonist protocol was used exclusively in four of them, while in the remaining two both GnRH agonists and antagonists were used (Kwan et al., 2014). Thus, it is not known whether the recommendation is valid in patients treated exclusively with GnRH antagonists.

The Cochrane meta-analysis was updated in 2021 (Kwan et al., 2021), however, no new studies were identified. The evidence based on the six trials identified in 2014 remained unchanged.

ULTRASOUND AND PROGESTERONE MEASUREMENTS OR ULTRASOUND AND LH MEASUREMENTS.

Currently no published evidence exists to allow for a recommendation to be formulated answering these questions.

ULTRASOUND AND COMBINATION OF HORMONAL MEASUREMENTS

Evidence

One RCT (114 women) reported no difference in OHSS (5.3% (3/57) vs. 7.0% (4/57)), pregnancy rate (22.2% vs. 25%), or number of oocytes retrieved (11.7±8.4 vs. 13.4±7.5) when monitoring was performed with ultrasound with or without hormonal measurements (Golan et al., 1994). Similarly, a more recent RCT (63 women) reported no difference in clinical pregnancy rate (40.0% (12/30)) vs. 57.5% (19/33)) or number of oocytes retrieved (10.0±5.5 vs. 11.7±8.0) with ultrasound and hormone panel monitoring compared with ultrasound only (Wiser et al., 2012). Furthermore, no cases of OHSS were reported in either the study or control group (Wiser et al., 2012).

Recommendation

The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring is probably not recommended. [2019]	Conditional ⊕◯◯◯

Justification

According to one RCT, monitoring of the stimulation phase by using hormonal panel assessments (oestradiol, LH, progesterone) and ultrasound is not beneficial in terms of efficacy and safety over monitoring by ultrasound alone in terms of efficacy and safety. The addition of hormonal assessments in the monitoring does not appear to increase the probability of pregnancy, the number of COCs retrieved, or to decrease the probability of OHSS or cycle cancellation for high response.

In the two studies, pituitary suppression was performed with GnRH agonists (Golan et al., 1994) or either GnRH agonists/antagonists (Wiser et al., 2012). Thus, it is not known whether the recommendation is valid in patients treated exclusively with GnRH antagonists.

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13. Endometrial thickness

PICO Question: Does monitoring of endometrial thickness affect the efficacy and safety?

Human endometrium has a key role in implantation process. Adequate endometrial development is required for pregnancy to occur. Thin endometrium on ultrasound during ovarian stimulation has been thought to be associated with poor success rates after IVF, even in the absence of prior intrauterine surgery or infection. At present, results from studies that investigated the relationship between endometrial thickness (EMT) and IVF outcomes are conflicting (Kasius et al., 2014). A meta-analysis by Kasius *et al.* reported a thin endometrium (≤7 mm) in 2.4% (260/10,724) of patients (Kasius et al., 2014). A more recent retrospective study reported 11% (57/517) of patients presenting with thin endometrium in ICSI cycles (Coelho Neto et al., 2015). However, in a large retrospective study by Holden *et al.* the proportion of patients with thin endometrium <7mm was 5.5% (347/6331) in IVF cycles (Holden et al., 2017).

Evidence

There are no studies comparing monitoring endometrial thickness compared to no monitoring, which would be the ideal study to answer this question. Alternatively, we looked at studies investigating whether endometrial thickness is predictive for implantation and live birth.

A meta-analysis combining 22 prospective and retrospective studies (10,724 patients and cycles) and several more recent studies found EMT having little to no discriminatory capacity for clinical pregnancy (Table 9) (Griesinger et al., 2018, Kasius et al., 2014, Lamanna et al., 2008, Rehman et al., 2015, Shakerian et al., 2021, Zhao et al., 2014). In addition, the study by Griesinger *et al.* reported that the independent contribution of EMT (assessed on day of embryo transfer) to live birth likelihood is small and may result from (undetermined) confounding factors. If EMT indeed is an independent factor affecting outcome, this finding implies that at a baseline live birth rate of 20% an increase of 2 mm in EMT should result in an increase of the live birth rate of ~1.6% (Griesinger et al., 2018).

Table 9: Accuracy of EMT in predicting pregnancy outcome

Predictive power of EMT on pregnancy outcome

Study	Cohort (n)	ROC-AUC
Kasius 2014	10.724 women and cycles	0.56
Other studies:		
Lamanna 2008	685 women	<0.70
Zhao 2014	3319 women	0.60
Rehman 2015	282 women	0.88
Griesinger 2018	1483 women	0.53

A meta-analysis[23] combining 30 cohort studies (9 prospective and 21 retrospective) including 88,056 cycles reported that women with lower EMT had a lower chance of clinical pregnancy than those with a higher EMT (OR 0.61, 95% CI 0.52-0.70) irrespective of fresh or frozen embryo transfer (Gao et al., 2020). When looking only at the prospective studies with fresh transfer and a cutoff value of >8 mm, no significant association between EMT and pregnancy rates were found. Similar results were found when pooling the 11 studies reporting on live birth rate/ongoing pregnancy rates, with a lower chance of live birth/ongoing pregnancy with lower EMT versus higher EMT (OR 0.60, 95% CI 0.48-0.73). Again, no association was found when only including prospective studies with fresh embryo transfer. Furthermore, there was no significant association between EMT and incidence of abortion rate (OR 1.33, 95% CI 0.98-1.80).

Several studies not included in the meta-analysis also reported a significantly lower probability of conceiving with EMT <8 mm as compared to EMT >8 mm (Table 10) (Aydin et al., 2013, Gallos et al., 2018, Rehman et al., 2015).

Table 10: Probability of pregnancy with thin endometrium.

Probability of pregnancy with EMT

Study	Cohort (n)	<8 mm	>8 mm
Gao 2020	88.056 cycles	OR 0.61, 95% CI 0.52-0.70	
Gallos 2018	45.279 cycles	15.6%	33.1%
Rehman 2015	282 women	5%	57.2%
Aydin 2013	593 women	7.1%	35.5%-43.9%

A large retrospective cohort study (3319 women) reported significant thicker EMT on the hCG day in the clinical pregnancy group compared with the not pregnant group (11.0±2.2 vs. 10.3±2.2 mm) (Zhao et al., 2014). In contrast, a large prospective study in 435 women reported no difference in endometrial thickness between pregnant and non-pregnant patients (11.2 mm (9.8-12.7) vs. 11.1 mm (9.5-12.9) (Zhang et al., 2016).

The thinnest endometrial thickness at which pregnancy occurred was 3.7 mm, in the study by Holden *et al*. and 5.6 mm in the study by Coelho Neto *et al*. Both pregnancies resulted in a live birth (Coelho Neto et al., 2015, Holden et al., 2017).

Recommendations

Routine monitoring of endometrial thickness during ovarian stimulation is probably not recommended. [2019]	Conditional ⊕◯◯◯

[23] The meta-analysis from Kasius 2014 cited here in the 2019 version was replaced by a more recent meta-analysis. Data from the studies by Wu *et al*., 2014, Yuan *et al*., 2016, Ribeiro *et al*., 2018 - previously cited in table 9 - are included in the meta-analysis by Gao *et al*. 2020 and therefore not mentioned separately anymore.

The guideline group suggests performing a single measurement of the endometrium during ultrasound assessment on the day of triggering or oocyte pick-up to counsel patients on potentially lower pregnancy chance. [2019]	GPP

Justification

There are indications that thin endometrium is related to lower ongoing/clinical pregnancy chances as an independent factor. This condition of thin endometrium occurs infrequent (2-5%). Interventions to correct thin EMT have little rational basis and should be abandoned until contrary evidence arises.

There are indications that thin endometrium is also associated with obstetric complications, even though rare (Lai et al., 2024, Oron et al., 2018). These observations, however, are only supported by a few retrospective cohort studies and the evidence is not solid.

A single ultrasound assessment is necessary to identify patients with very thin or very thick EMT, and appropriate diagnostic work-up should be done.

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14. Criteria for final oocyte maturation

PICO Question: Is the outcome of ovarian stimulation dependent on the criteria for final oocyte maturation?

Follicle size

Evidence

A meta-analysis including 7 RCTs investigated the effect of postponing final oocyte maturation by 24-48 hours. There was no significant difference in live birth rate (3 RCT, RR 1.14, 0.46-2.83, 354 women) or ongoing pregnancy rate per oocyte pick-up (4 RCT, RR 0.97, 95% CI 0.54–1.74, 743 women) between early hCG and the late hCG group. However, significantly more oocytes were retrieved in late hCG group than in early hCG group (4 RCT, MD 1.2, 95% CI 1.11–1.30, 743 women) (Chen et al., 2014).

In the meta-analysis there was one study comparing triggering at different follicular sizes, the only trial identified by the literature search investigating this research question. In this RCT (190 women), triggering was performed when the leading follicle reached either 18 or 22 mm. There was no significant difference in live birth rate when trigger was administered when the leading follicle was 22 mm (35% (34/97)) compared to 18 mm (23% (21/93)) (RR 1.6 (0.98–2.47)). However, more women reached an ongoing pregnancy (38% (37/97)) compared with the 18-mm group (24% (22/93)) (RR 1.6, 95% CI 1.03–2.5) and significantly more oocytes were retrieved (11.7 ± 5.7 vs. 9.7 ±4.1) (Mochtar et al., 2011).

Recommendations

The association of follicle size as a triggering criterion with outcome has not been sufficiently studied. Physicians may choose the follicle size upon which final oocyte maturation is triggered on a case to case basis. [2019]	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 day of pursued trigger, duration of stimulation, embryo transfer strategy, 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 16-22 mm. [reworded]	GPP

Justification

The available studies have compared, except for one (Mochtar et al., 2011), not different follicle sizes as trigger criteria but postponing hCG administration after a given sonographic follicular criterion had been reached. Later hCG administration is associated with the retrieval of more oocytes. An effect on any other efficacy or safety or patient-related outcome was either not studied or not demonstrated in a consistent (e.g. homogenous) way across studies.

OESTRADIOL LEVEL

Evidence

There are no interventional studies investigating triggering based on oestradiol levels.

Recommendations

The GDG does not recommend to base timing of final oocyte maturation triggering on oestradiol levels alone. [2019]	GPP

Justification

No interventional study has been performed assessing the use of serum oestradiol as a criterion for when to trigger final oocyte maturation. Serum oestradiol levels during ovarian stimulation vary depending on the size of the growing follicular cohort, the distribution of follicles between different size classes within the growing cohort as well as the endocrine situation of the patient and the endocrine milieu of the stimulation cycle. The association of the serum oestradiol levels with clinical outcomes and OHSS risk has been studied in several observational studies, but management recommendations cannot be derived from these observational data.

OESTRADIOL/FOLLICLE RATIO

Evidence

There are no interventional studies investigating triggering based on the oestradiol/follicle ratio.

Recommendations

The GDG does not recommend to base timing of final oocyte maturation on oestradiol/follicle ratio alone. [2019]	GPP

Justification

No interventional study has been performed assessing the use of serum oestradiol-to-follicle ratio as a criterion for when to trigger final oocyte maturation. The oestradiol-to-follicle ratio will vary depending on the size of the growing follicular cohort, the distribution of follicles between different size classes within the growing cohort as well as the endocrine situation of the patient and the endocrine milieu of

the stimulation cycle. The association of the oestradiol-to-follicle ratio with clinical outcomes has been studied in several observational studies, but management recommendations cannot be derived from these observational data.

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15. Hormonal assessment on the day of final oocyte maturation

PICO Question: Is hormonal assessment on the day of final oocyte maturation recommended?

hCG triggered cycles

Progesterone

Evidence

A systematic review and meta-analysis, including 55,199 fresh embryo transfer cycles from 63 prospective and retrospective studies, reported that serum progesterone levels above 0.8 ng/mL on the day of hCG administration was associated with significantly decreased odds of live birth/ongoing pregnancy rate (OR 0.72, 95% CI 0.56-0.94; OR 0.64, 95% CI 0.53-0.77; OR 0.62, 95% CI 0.57-0.69; OR 0.67, 95% CI 0.55-0.81 for serum progesterone levels of 0.8-1.1 ng/mL, 1.2–1.4 ng/mL, 1.5–1.75 ng/mL, and 1.9–3.0 ng/mL, respectively) (Venetis et al., 2013). A meta-regression analysis suggested that the type of patient population (i.e., low responders, normal responders, high responders), the developmental stage of embryo at transfer (cleavage versus blastocyst stage), or the study design (retrospective vs prospective) did not modulate the conclusions. Based on an analysis of 37 studies reporting the number of oocytes collected, the mean number of cumulus oocyte complexes retrieved was significantly increased in patients with progesterone elevation compared with those without progesterone elevation. This finding was consistent across all progesterone elevation threshold groups, ranging from +1.9 in the 1.2–1.4 ng/mL to +3.1 COCs in the 1.5–1.75 ng/mL group (Venetis et al., 2013).

A retrospective study including 4,651 patients undergoing their first IVF cycles reported significantly lower cumulative live birth rates in patients with low ovarian response (≤5 oocytes collected), intermediate ovarian response (6-19 oocytes collected) and high ovarian response (>19 oocytes collected), when serum progesterone levels on the day of HCG trigger was >1.5 ng/mL, 2.24 ng/mL and 2.5 ng/mL, respectively. Adjusted analyses demonstrated an inverse relationship between serum progesterone levels on the day of HCG trigger and cumulative live birth rates in all groups (Bu et al., 2014).

Based on sixteen studies, the same meta-analysis reported that serum progesterone elevation on the day of HCG trigger in the stimulation cycle was not associated with the probability of pregnancy achievement in a subsequent frozen–thawed cycle. This finding was consistent across all progesterone threshold groups (Venetis et al., 2013).

A multicentre retrospective study compared cumulative live birth rate over 24 months following a freeze all approach between patients with serum progesterone levels <1.50 ng/mL and >1.50 ng/mL on the day of hCG trigger. There were 471 patients in each group, who were matched for age and oocyte yield. Cumulative LBR was similar the two study groups (29.3% and 28.2%) (Racca et al., 2021).

Recommendations

It is probably recommended to measure serum progesterone levels on the day of final oocyte maturation in cycles aimed for a fresh embryo transfer. [2025]	Conditional ⊕◯◯◯

If serum progesterone levels are high, the patient should be counselled about potentially lower ongoing pregnancy/live birth rates. The decision to defer embryo transfer should include other factors (number of oocytes, number of embryos, and embryo quality). [2025]	GPP

Justification

Patients cannot be randomized to have different serum progesterone levels on the day of hCG trigger so decisions have to be based on observational studies. Observational studies consistently report decreased live birth/ongoing pregnancy rate and even suggest a gradient effect, i.e., higher progesterone levels are associated with lower ongoing pregnancy/live birth rates, supporting a causal relationship. While a 2024 systematic review and meta-analysis reported similar results for day 3 transfers, live birth and clinical pregnancy rates were not significantly affected by elevated progesterone in a subgroup analysis limited to day 5 transfers (Lim et al., 2024). However, the pooled analysis result seems to be possibly shifted by one retrospective study, which has a small sample size, an unusually high rate of progesterone elevation and unusually low rate of live birth and clinical pregnancy rate in the non-progesterone elevation group (Huang et al., 2015). Thus, the GDG acknowledges some controversy but still holds the opinion that elevated progesterone would affect fresh day 3 and day 5 similarly. An indirect study suggest that effect of elevated progesterone levels is mediated through endometrial advancement and resultant embryo – endometrium asynchrony, not through a perceivable effect on oocyte developmental potential (Racca et al., 2021). Thus, deferring embryo transfer to a frozen embryo transfer cycle without endometrial advancement seems to provide similar live birth rates with non-progesterone elevated cycles. Given that a solution exists for the problem it is justifiable to diagnose progesterone elevation and forfeit a fresh embryo transfer as necessary.

OESTRADIOL

Evidence

A systematic review and meta-analysis, including 3 cohort studies and 641 cycles, investigated whether the probability of live birth/ongoing pregnancy (≥12 weeks of gestation) or clinical pregnancy (up to 6–8 weeks of gestation) after ovarian stimulation for IVF, using gonadotropin-releasing hormone (GnRH) analogues and gonadotrophins is associated with serum oestradiol levels on the day of triggering final oocyte maturation with hCG (Karatasiou et al., 2020). While the odds of achieving a clinical pregnancy

gradually declined with higher oestradiol levels, demonstrating a gradient effect, the difference was not statistically significant.

A retrospective study including 1,141 non-PCOS patients with an AFC of >7 who underwent a long luteal GnRH agonist or a flexible GnRH antagonist protocol reported that peak serum oestradiol level on the day of hCG administration was not associated with cumulative live birth rate in a multivariable analysis (OR 0.995, 95% CI 0.98-1.01) (Zhang et al., 2019). A quantitative analysis suggested that until a peak oestradiol level of <2,185 pg/ml, the cumulative LBR statistically significantly increased by about 12% with every 100 pg/ml increase of the peak oestradiol level. Between peak oestradiol levels of 2,185 and 6,136 pg/ml, the cumulative LBR only slightly decreased (0.4% per 100 pg/mL increase in peak oestradiol). When the peak oestradiol level that was higher than 6,136 pg/mL, a more prominent decrease in cumulative LBR was observed (10% per 100 pg/ml increase in peak E2), but this was short of statistical significance (Zhang et al., 2019).

A retrospective study divided 1,771 fresh embryo transfer cycles following ovarian stimulation with a long luteal GnRH agonist or a GnRH antagonist protocol into six groups based on peak oestradiol levels on the day of hCG administration as the following; ≤1000 pg/mL, 1001–2000 pg/mL, 2001–3000 pg/mL, 3001–4000 pg/mL, 4001–5000 pg/mL, and > 5000 pg/mL (Li et al., 2019). Clinical pregnancy rate gradually increased from <100 pg/mL group to 4001–5,000 pg/ml and declined in the >5,000 pg/mL group. Similar pattern was observed for number of MII oocyte counts.

A retrospective study included 3,393 patients younger than 40 years undergoing IVF with a long luteal GnRH agonist protocol (Wang et al., 2017). Cycles with a serum oestradiol level >3,757 pg/mL on the day of HCG trigger were reported to have a significantly higher mean number of oocytes (14.4±5.3 vs. 7.4±3.9), 2PN oocytes (9.56±4.18 vs. 4.98±2.97), good-quality embryos (5.69±3.45 vs. 2.96±2.27), as well as higher risk of OHSS (3.9% vs 0.6%). Live birth (47.4% vs. 43%) and clinical pregnancy (57.2% vs. 52.1%), were significantly higher in the high oestradiol group (Wang et al., 2017).

Recommendations

It is not recommended to routinely measure serum oestradiol levels on the day of hCG trigger in ovarian stimulation cycles with an intent for a fresh embryo transfer. [2025]	Strong ⊕◯◯◯

Justification

Patients cannot be randomized to have different serum oestradiol levels on the day of hCG trigger, therefore decisions have to be based on observational studies. Observational studies consistently suggest that serum oestradiol levels are poor predictors of live birth/ongoing pregnancy rate beyond an association between serum oestradiol levels and oocyte yield. Serum oestradiol levels are poor predictors of obstetric and neonatal adverse events. While serum oestradiol level is strongly correlated with follicle count, serum oestradiol levels considerably overlap between patients who develop moderate severe OHSS following a hCG trigger and fresh embryo transfer.

LH

Evidence

A retrospective study including 3,059 patients who underwent a fresh embryo transfer following ovarian stimulation with an hCG triggered GnRH antagonist protocol, divided patients in three categories of anticipated ovarian response (low: AMH <1.1 ng/mL or AFC <5 or previous low response; normal: AMH>1.1 ng/mL or AFC >5 and regular menstrual cycles) and PCOS (as per Rotterdam criteria)). Patients in each anticipated ovarian response category were categorized according to quartiles of serum LH levels on the day of the trigger (<25th percentile, 25th to 75th percentile and >75th percentile). Compared to patients with anticipated normal ovarian response and LH levels >75th percentile, patients in <25th percentile (adjusted OR 0.662, 95%CI 0.508-0.863) and 25th-75th percentile categories (adjusted OR 0.791, 95% CI 0.633-0.988) had significantly lower live birth rates than those in the >75th percentile category. Likewise, patients with PCOS and LH levels <25th percentile also had significantly lower live birth rates in comparison to patients with LH levels >75th percentile (adjusted OR 0.479, 95% CI 0.277-0.828). Live birth rates were not correlated with LH quartiles in patients with an anticipated low ovarian response (Zhou et al., 2023).

A retrospective study including 4,502 fresh embryo transfers following ovarian stimulation with an hCG triggered short GnRH agonist protocol, divided patients in five categories based on serum LH levels on the day of HCG trigger (Group A: LH ≤0.5 IU/L, Group B: 0.5 IU/L < LH ≤1.2 IU/L, Group C: 1.2 IU/L < LH ≤2.0 IU/L, Group D: 2.0 IU/L < LH ≤5.0 IU/L, Group E: LH>5 IU/L). Regression analyses showed that each unit increase in LH levels on the day of HCG trigger was inversely correlated with the number of oocytes retrieved (adjusted OR -0.351, 95% CI -0.453 to -0.249). However LH levels were not associated with live birth rates (Zhang et al., 2022).

A retrospective study included 9,334 fresh ART cycles following ovarian stimulation with an hCG triggered long luteal GnRH agonist or a flexible GnRH antagonist (Luo et al., 2023). Cycles were divided in three categories based on tertiles of serum LH levels on the day of hCG trigger. Multivariable regression analysis suggested that higher LH levels were associated with significantly higher live birth and clinical pregnancy rates with both protocols. However, in GnRH antagonist cycles, the difference was only significant for when comparing the third tertile with the first tertile (Luo et al., 2023).

Recommendation

It is not recommended to measure serum LH levels on the day of hCG trigger in ovarian stimulation cycles aimed for a fresh embryo transfer. [2025]	Strong	⊕◯◯◯

Justification

The available studies are limited by retrospective design and complicated analytical approach using different thresholds. Their results are inconsistent and do not provide actionable conclusions.

GnRH agonist triggered cycles

Progesterone

Evidence

A retrospective study including 1,484 GnRH agonist triggered PPOS cycles reported that serum progesterone levels on the day of trigger were not associated with the risk of inadequate response to the agonist trigger defined as a serum LH level <15 IU/L, 12 h after the agonist trigger (Lu et al., 2016).

A retrospective study including 3,334 agonist triggered GnRH antagonist cycles reported similar serum progesterone levels on the day of agonist trigger between cycles with an adequate and with an inadequate response, defined as the ratio between the total number of oocytes retrieved and the number of follicles with a mean diameter >10 mm on the day of/prior to the trigger <45% (1.3±0.8 vs. 1.4±0.9 ng/ml, respectively) (Popovic-Todorovic et al., 2019).

Oestradiol

Evidence

A retrospective study including 1,484 GnRH agonist triggered PPOS cycles reported significantly different serum oestradiol levels on the day of trigger between cycles with an adequate and inadequate response to the GnRH agonist trigger defined as a serum LH level <15 IU/L, 12 h after the agonist trigger (2,753.23 ± 1,616.34 vs. 1,906.41 ± 1,656.87) (Lu et al., 2016).

A retrospective study including 3,334 GnRH agonist triggered GnRH antagonist cycles reported significantly different serum oestradiol levels on the day of trigger between cycles with an adequate and with an inadequate response, defined as the ratio between the total number of oocytes retrieved and the number of follicles with a mean diameter >10 mm on the day of/prior to the trigger <45% (2796.2±1752.6 vs. 2277.5±1728.1 pg/mL, respectively) (Popovic-Todorovic et al., 2019).

A retrospective study including 502 GnRH agonist triggered GnRH antagonist cycles reported that serum oestradiol levels on the day of trigger were significantly different between cycles with and without an adequate post-trigger LH response defined as serum LH level >15 IU/L 12 hours after the GnRH agonist trigger (3242 ± 1233 vs. 2564 ± 1257 pg/ml, respectively) (Kummer et al., 2013).

LH

Evidence

A retrospective study including 1,747 GnRH agonist triggered GnRH antagonist cycles reported that serum LH level on the day of trigger was not associated the risk of low oocyte maturation rate, defined as <75% of all oocytes collected being at MII stage, or the risk of having a low oocyte recuperation rate, defined as the ratio of collected oocytes over the number of follicles measuring ≥12 mm on the day of trigger below the 10th percentile (Gambini et al., 2024).

A retrospective study including 1,484 GnRH agonist triggered PPOS cycles reported that serum LH levels on the day of trigger were not associated the risk of inadequate response to the agonist trigger defined as a serum LH level <15 IU/L 12 h after the agonist trigger (Lu et al., 2016).

A retrospective study including 3,334 GnRH agonist triggered GnRH antagonist cycles reported similar serum LH levels on the day of agonist trigger between cycles with an adequate and with an inadequate response, defined as the ratio between the total number of oocytes retrieved and the number of follicles with a mean diameter >10 mm on the day of/prior to the trigger <45% (Popovic-Todorovic et al., 2019).

A retrospective study including 502 GnRH agonist triggered GnRH antagonist cycles reported that serum LH levels on the day of trigger were significantly different between cycles with and without an adequate post trigger LH response defined as serum LH level >15 IU/L 12 hours after the agonist trigger (2.1±1.9 vs 1±1.4 IU/L, respectively) (Kummer et al., 2013).

15.2.4 Overall recommendation

Recommendation

It is not recommended to measure serum oestradiol, progesterone or luteinizing hormone levels on the day of a GnRH agonist trigger in freeze-all cycles. [2025]	Strong	⊕◯◯◯

Justification

Serum levels of oestradiol, progesterone and luteinizing hormone levels largely overlap in cycles with and without an adequate response to a GnRH agonist trigger, hence they do not have a discriminatory value. Patients at risk of inadequate response, e.g. patients with hypogonadotropic hypogonadism, prolonged combined contraceptive use, etc. can be identified at the beginning of the stimulation cycle. When a fresh embryo transfer is not intended serum progesterone levels on the day of trigger would not affect live birth rates with a subsequent frozen embryo transfer. While the studies reporting similar cumulative live birth rates and live birth rates after the first frozen embryo transfer between stimulation cycles with and without progesterone elevation were not performed exclusively GnRH agonist triggered cycles, available evidence does not support a carryover effect of endometrial advancement due to progesterone elevation in the stimulation cycle.

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16. Criteria for cycle cancellation

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

Since the year 1983 –when the term ,,poor responder" was described for the first time (Garcia et al., 1983), no international consensus regarding the definition of a poor response was available and different definitions were used. In 2011, the European Society of Human Reproduction and Endocrinology (ESHRE) defined poor response as: 'cycle cancellation or retrieval of fewer than four oocytes with a conventional ovarian stimulation protocol' (Ferraretti et al., 2011).

Similarly, there is no international consensus definition for high response, which would help to identify women who can develop OHSS and allow undertaking interventions to avoid developing the condition.

Low oocyte yield

Evidence

The occurrence of low response is reported to vary between 5.6% and 35.1% or 9% to 24 % depending on the definition of low response (Oudendijk et al., 2012). The decision making to stop the treatment, or to encourage to start another cycle is always difficult in respect to low number of oocytes and should be individually taken. Other factors, which influence pregnancy rate (e.g. age of patient) and burden of therapy, should be taken into account. The data also demonstrated that the pregnancy could still occur even if in the first cycle the women is defined as low responder (Baka et al., 2006).

In a meta-analysis combining prospective and retrospective cohort studies, the pooled estimate of pregnancy rate for poor responders was 14.8%, compared with 34.5% for normal responders (6 cohort studies, n=14338 women/cycles) (Oudendijk et al., 2012). The chance of pregnancy in respect to number of oocytes varied across studies. Women with 1 oocyte retrieved had 0-7%, 2 oocytes 4.3-15.2%, 3 oocytes 8.7-15.6%, and 4 oocytes 11.5–18.6% (4 cohort studies, 8744 women/cycles) (Oudendijk et al., 2012). Finally, in one study where 5 oocytes were obtained, pregnancy rate was up to 22 % (Oudendijk et al., 2012, Timeva et al., 2006). A more recent, large retrospective study reported a predicted live birth rate of 2% (n=541 cycles, 95% CI 2-3%) in women >40 years of age with one oocyte retrieved (Sunkara et al., 2011).

In a retrospective study, it was examined whether IVF stimulation that results in one or two mature follicles should proceed to oocyte retrieval. The treatment outcomes were stratified in age groups (≤34, 35-39, ≥40 years) (Shrem et al., 2022). The number of MII oocytes retrieved was 1.7±0.9 , which did not differ between the age groups (<34: 1.8±0.7, 35-39: 1.7±1.0, ≥40: 1.7±0.8). There was however a significant difference in live birth rate per cycle between women ≤ 34 years (15.6%) and 35-39 years (6.5%) and ≥40 years (2.7%). In regression models, for LB, age was the only significant predictor. The change in pregnancy rate or LB as a function of age is dependent on AFC, suggesting that AFC is an important independent predictor which is more significant as age decrease.

A large prospective study (1012 women, long GnRH agonist protocol) reported no live birth in women with AFC <4 (0%), but a live birth rate of 5% with an AFC of 4 (Jayaprakasan et al., 2012). The presence of one or two follicles in poor responders still could lead to obtain pregnancy. A large retrospective

study (800 cycles, long GnRH agonist/GnRH antagonist protocols) in poor responders with 1 or 2 follicles >12 mm after ovarian stimulation, reported a clinical pregnancy rate of resp. 5.4% (12/223) and 9.2% (53/577) and an ongoing pregnancy rate of resp. 4.5% (10/223) and 7.6% (44/577) (Nicopoullos and Abdalla, 2011). A more recent, large retrospective study (256.381 cycles) reported a live birth rate of 17% when the number of retrieved oocytes was between 0-5 (Steward et al., 2014).

HIGH OOCYTE YIELD

Evidence

The incidence of severe OHSS reported in clinical studies varies from 2% (Papanikolaou et al., 2006) to almost 9% (Toftager et al., 2016). The incidence of high response varied from >14 to >16 retrieved oocytes (Broer et al., 2013). It has been demonstrated in several prospective studies that a high number of growing follicles is an independent predictor of OHSS (Jayaprakasan et al., 2012, Papanikolaou et al., 2006).

A large prospective study with 2362 women advised cycle cancellation with >30 follicles of 12 mm during OS with long GnRH agonist protocol (Mathur et al., 2000). In a large prospective cohort study with 1801 women (2524 cycles), the threshold of ≥18 follicles ≥11 mm during OS with GnRH antagonist protocol predicted severe OHSS with 83% sensitivity rate with a specificity as high as 84% (Papanikolaou et al., 2006). According to the SART registry, analysis of 256.381 cycles revealed that retrieval of >15 oocytes significantly increases the risk of OHSS and does not lead to an increased live-birth rate in fresh cycles (Steward et al., 2014). A recent large retrospective analysis of the Engage, Ensure and Trust trials found that the threshold of 19 follicles of ≥11 mm on hCG day predicted moderate to severe OHSS with 62.3% sensitivity and 75.6% specificity (ROC-AUC 0.73), and predicted severe OHSS with 74.3% sensitivity and 75.3% specificity (ROC-AUC 0.77) in GnRH antagonist protocol (Griesinger et al., 2016).

There was a strong association between the number of oocytes and LBR; LBR rose with an increasing number of oocytes up to 15, plateaued between 15 and 20 oocytes and steadily declined beyond 20 oocytes. The LBR for women with 15 oocytes retrieved in age groups 18–34, 35–37, 38–39 and 40 years and over was 40, 36, 27 and 16% respectively (Sunkara et al., 2011).

Recommendations

A low response to ovarian stimulation alone is not a reason to cancel a cycle. [2019]	Strong	⊕◯◯◯

The physician should counsel the individual unexpected low responder regarding pregnancy prospects and decide individually whether to continue this cycle. [updated]	GPP

In GnRH agonist cycles with an ovarian response of ≥19 follicles of ≥11 mm, there is an increased risk of OHSS and preventative measures are recommended, which should include primarily cancelling final oocyte maturation trigger. [updated]	Strong	⊕◯◯◯

In GnRH antagonist cycles, withholding GnRH agonist triggering may still be considered in women with extremely high ovarian response. [2025]	GPP

Justification

Reported pregnancy rates among low responders to ovarian stimulation differ between 0-max reported 18%. These differences could be explained by the exact number of oocytes retrieved, as well as the age of the patient and indication for treatment. Although pregnancy rates may be low, they are not absent per se.

For an expected low responder, a cycle should not be cancelled due to low response. The GDG assumes that pregnancy prospects, costs etc. have been considered before starting the ovarian stimulation cycle.

For an unexpected low responder, the GDG recommends the physician to counsel patients individually regarding pregnancy prospects and the decision to continue this cycle.

Regarding a high response there are also no solid criteria to cancel a cycle. A high response identifies women most at risk for OHSS. The risk of OHSS and the number of growing follicles, is not a linear connection. There is probably a threshold effect, however, this is currently unknown. The current evidence comes from studies in GnRH antagonist cycles. The study by Griesinger *et al*. did not include PCOS patients, in contrast, the study by Papanikolau *et al.* did, explaining the lower threshold used in that study. Therefore, preventive measures are recommended which should include cycle cancellation.

In GnRH antagonist cycles, withholding GnRH agonist triggering may still be considered in women with extremely high ovarian response (Berkovitz-Shperling et al., 2024). The GDG could not provide a threshold for this extremely high ovarian response, because the significance of this response could vary based on individual patient clinical characteristics.

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PART F: Triggering ovulation and luteal support

17. Triggering of final oocyte maturation

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

Urinary (uhCG) vs Recombinant Human chorionic gonadotrophin (rhCG)

Evidence

A Cochrane systematic review and meta-analysis found no difference in live birth/ongoing pregnancy rate (7 RCT, OR 1.15, 95% CI 0.89-1.49, 1136 women), moderate to severe OHSS (3 RCT, OR 1.76, 95%CI 0.37-8.45, 417 women), moderate OHSS (1 RCT, OR 0.78, 95% CI 0.27-2.27, 243 women), mild to moderate OHSS (2 RCT, OR 1.00, 95% CI 0.42-2.38, 320 women), undefined OHSS (3 RCT, OR 1.18, 95% CI 0.50-2.78, 495 women) or number of oocytes (12 RCT, MD−0.11, 95% CI −0.70 to 0.47, 1744 women) between recombinant and urinary hCG when used for triggering final oocyte maturation (Youssef et al., 2016).

One RCT including 100 women compared 10,000 IU with 5000 IU of urinary hCG for triggering final oocyte maturation in the long GnRH agonist protocol (Shaltout et al., 2006). There was no significant difference in pregnancy rate (not specified) (35.4% vs. 33.3%, incidence of OHSS (8.3% (4/48) vs. 2% (1/50)) or number of oocytes retrieved (7.4±3 vs. 7±3.5) between 10,000 IU and 5000 IU of uhCG for final oocyte maturation (Shaltout et al., 2006).

One RCT including 80 PCOS patients randomized to receive 10,000 IU, 5000 IU, or 2500 IU of uhCG for triggering final oocyte maturation in the GnRH antagonist protocol as soon as 3 or more follicles of 17 mm or larger were present at ultrasound (Kolibianakis et al., 2007). There was no significant difference in ongoing pregnancy rate ((25.0% (7/28) vs. 30.8% (8/26) vs. 30.8% (8/26)), severe OHSS (1/28 vs. 1/26 vs. 0/26) or number of oocytes retrieved (median 14 vs. 11.5 vs. 9) between 10,000 IU, 5000 IU and 2500 IU uhCG (Kolibianakis et al., 2007).

One RCT including 180 women compared 500 µg with 250 µg recombinant hCG for triggering final oocyte maturation in the long GnRH agonist protocol (Madani et al., 2013). There was no significant difference in clinical pregnancy rate (34.5% (19/55) vs. 42.2% (19/45)), occurrence of OHSS (10% (6/60) vs. 6.7% (4/60)) or number of oocytes retrieved (12.25±5.30 vs. 12.40±6.44) between 500 µg and 250 µg rhCG (Madani et al., 2013).

Recommendation

The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation in ovarian stimulation protocols. [2019]	Strong ⊕⊕◯◯

A reduced-dose of 5.000 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. [2019]	Conditional ⊕◯◯◯

Justification

The Cochrane meta-analysis shows equal efficacy and safety for urinary and recombinant hCG. The grand majority of the trials (17 out of 18) included in the meta-analysis by Youssef *et al*. 2016, performed pituitary downregulation using a long GnRH agonist protocol, only one trial was performed using a GnRH antagonist protocol (Youssef et al., 2016). The evidence regarding antagonist protocol is inconclusive so the recommendation might not be applicable for GnRH antagonist cycles, although there is no evidence to suggest a difference in safety and efficacy.

Different doses of uhCG have been described in the literature ranging from 2.000 IU to 10.000 IU. According to 2 RCTs, a reduced-dose of urinary hCG (5.000 IU) does not appear to affect the probability of pregnancy compared to conventional dose (10.000 IU). Similarly, data from 1 RCT suggests that a low dose (250µg) of recombinant hCG does not appear to influence the probability of pregnancy as compared to a higher dose (500 µg). The probability of OHSS was reduced when lower doses of hCG were administered but this did not reach statistical significance in any of the 3 RCTs. Lower doses of hCG could be considered when an unpredicted high response has occurred, and GnRH long agonist protocol is applied.

RECOMBINANT LH (RLH) VS URINARY HCG (UHCG)

Evidence

The trials had administered different dosages of rLH which varied from 5000 IU (Manau et al., 2002) to 15000 IU and an additional 10000 IU three days post the first injection (2001).

The Cochrane meta-analysis, mentioned before, reported no difference in live birth/ongoing pregnancy rate (2 RCT, OR 0.95, 95% CI 0.51-1.78, 289 women), moderate OHSS (2 RCT, OR 0.83, 95% CI 0.40-1.70, 289 women) or number of oocytes retrieved (2 RCT, MD−1.33, 95%CI −3.26 to 0.60, 103 women) between rLH and uHCG when used for triggering final oocyte maturation (Youssef et al., 2016).

Recommendation

It is not recommended to administer recombinant LH for triggering final oocyte maturation. [2019]	Strong	⊕◯◯◯

Justification

The available evidence is currently very limited to allow solid conclusions to be drawn. There was large heterogeneity between the three trials included with respect to study methods. Therefore, we cannot recommend the use of rLH to trigger final oocyte maturation.

GnRH agonist trigger vs hCG

Evidence

A systematic review and meta-analysis, including 9 RCTs and 1277 women compared GnRH agonist to hCG for final oocyte maturation (Beebeejaun et al., 2024). There was no significant difference observed between hCG and GnRH agonist trigger for live birth rate (RR 0.82; 95% CI 0.59–1.13,3 RCT, 723 women) or clinical pregnancy rate (RR 1.15; 95% CI 0.81–1.63; 3 RCT, 687 women).

Recommendation

The use of GnRH agonist for final oocyte maturation is not recommended in the general IVF/ICSI population with fresh transfer, regardless of luteal phase support (with or without LH-activity). [updated]	Strong	⊕⊕◯◯

Justification

Current evidence shows a disadvantage in ongoing/clinical pregnancy rate with GnRH agonist and conventional luteal support as compared to hCG in normal responders.

Recent evidence shows that this disadvantage could be overcome by adding LH-activity to the LPS, however, this effect needs to be studied in a large RCT. Thus, with the current knowledge we cannot recommend GnRH agonist triggering with modified LPS for the overall IVF/ISCI population.

There were no RCTs comparing GnRH agonist to hCG triggering in PPOS protocol. The only available evidence was a retrospective cohort study, which is insufficient evidence to formulate a recommendation.

Although GnRH agonist trigger is associated with decreased OHSS rates, it is associated with low levels of endogenous LH secretion after triggering. In a retrospective cohort study, including 1747 patients, patients were divided into <10^{th} percentile of oocyte recovery rate (n=139) and >10^{th} percentile oocyte recuperation rate (1281). Lower ovarian reserve and lower LH level 12-h post-triggering were predictive of lower ORR (OR 0.80 [95% CI 0.68–0.94]) and 0.80 [0.73–0.89], respectively (Gambini et al., 2024). In another retrospective cohort study, including 14066 patients, 51 patients were found to have empty

follicle syndrome (EFS). After adjusting for confounding factors, PCOS was found to be a significant risk factor for EFS (aOR = 2.67; 95% CI 1.47-4.83) (Luo et al., 2024).

GnRH agonist triggering for (predicted) high responder is discussed further in the guideline (chapter 19).

TRIPTORELIN 0.1 MG VS HIGHER DOSAGES

Evidence

One RCT including 165 oocyte donors compared different dosages (0.2 mg vs. 0.3 mg vs. 0.4 mg) of triptorelin for final oocyte maturation in GnRH antagonist protocol and reported no significant differences in number of oocytes retrieved (18.4±8.8 vs. 18.7±8.9 vs. 17.8±10.7) or mature oocytes (16.0±8.5 vs. 15.9±7.8 vs. 14.7±8.4). One case of OHSS was reported in the 0.3 mg group (Vuong et al., 2016).

In a retrospective cohort study, including 131 patients at risk of OHSS, different dosages of triptorelin (0.1 mg, 0.2 mg and 0.4 mg) were given for final oocyte maturation (Lainas et al., 2019). No significant difference was observed in number of MII oocytes (21 (13) vs. 20 (6) vs. 20 (11),respectively).

Recommendation

If the GnRH agonist trigger with triptorelin is applied, dosages ranging between 0.1-0.4 mg can be chosen. [2019]	GPP

Justification

According to currently available evidence, no significant differences have been observed in metaphase II (MII) oocytes between the various doses of triptorelin used (0.1 mg to 0.4 mg). There are no studies investigating the direct comparison of hCG with different dosages of GnRH agonist trigger with triptorelin.

BUSERELIN 0.2 MG VS 0.5 – 1 – 2 MG

Evidence

There are no studies investigating the direct comparison of hCG with different dosages of GnRH agonist trigger with buserelin. No controlled studies or RCT could be found comparing different dosages of Buserelin for final oocyte maturation. Therefore, no recommendation can be formulated regarding optimal dosage.

LEUPROLIDE 0.15 MG VS 0.5 – 1 – 2 - 4 MG

Evidence

There are no studies investigating the direct comparison of hCG with different dosages of GnRH agonist trigger with leuprolide. No controlled studies or RCT could be found comparing different dosages of Leuprolide for final oocyte maturation. Therefore, no recommendation can be formulated regarding optimal dosage.

DUAL AND DOUBLE TRIGGER

Although GnRH agonist trigger is associated with decreased OHSS rates, it is associated with low levels of endogenous LH secretion after triggering, resulting in lower progesterone levels during the luteal phase. Several concepts of intensified luteal phase support have been formulated, among which the concept of dual and double trigger. The concept of a dual or double trigger has been proposed for cases characterized by low oocyte maturation, poor oocyte recovery, or low fertilization rates. Dual trigger is defined as the simultaneous administration of hCG and GnRH agonist for final oocyte maturation. Staggered coadministration of GnRH agonist and hCG for final oocyte maturation, the double trigger, was proposed as another trigger option, applying an interval of 12-24h.

DUAL TRIGGER

Evidence

A systematic review and meta-analysis[24] investigated the use of hCG and GnRH agonist (dual trigger) for final oocyte maturation and compared its efficacy to hCG in normal responders (Beebeejaun et al., 2024). Higher live birth rates were found with dual trigger (RR 1.31, 95% CI 1.00-1.70, 1 RCT, 496 women) (Beebeejaun et al., 2024, Zhou et al., 2022). However, the meta-analysis relied solely on the study by Zhou et al. (2022), which did not demonstrate a statistically significant difference in live birth rate following fresh embryo transfer between the dual trigger group and hCG group (36.8% vs. 13.6%, *P* = 0.082). Likewise, in frozen embryo transfers, no significant improvement in live birth rate was observed with dual trigger compared to hCG (32.6% vs. 27.9%, p = 0.537). No significant difference was found between dual trigger and hCG trigger for final oocyte maturation for clinical pregnancy rate (RR 1.20, 95% CI 0.89–1.60, 3 RCT, 613 participants).

In an RCT, participants with a normal ovarian reserve underwent ovarian stimulation for IVF/ICSI with final oocyte maturation triggered by either dual trigger (n=50) or hCG only (n=50) (Singh et al., 2023). No significant difference was observe in clinical pregnancy rate between dual trigger and hCG for final oocyte maturation (21% vs. 19.6%). No cases of OHSS were observed in either group.

An RCT compared hCG 6500 IU with dual trigger (6500 IU hCG+0.2 mg GnRH agonist) in 192 normal responder women (Eftekhar et al., 2017). There was no significant difference in ongoing pregnancy rate (22.9% (20/93) vs. 24.2% (24/99)) between hCG and dual trigger. However, significantly more oocytes were retrieved with dual trigger compared to hCG trigger (10.85± 4.71 vs. 9.35 ±4.35) (Eftekhar, et al., 2017).

In a retrospective cohort study one complete oocyte retrieval cycle (fresh+frozen) was compared for dual trigger and hCG trigger in the PPOS protocol in normal responders (Li et al., 2022). No significant difference was observed in cumulative live birth rate between dual trigger and hCG trigger only (40.72% (204/501) vs. 43.72% (247/565)).

<u>Low responders</u>

A sub-analysis of a systematic review and meta-analysis investigated the use of hCG and GnRH agonist (dual trigger) for final oocyte maturation and compared its efficacy to hCG in poor responders (He et

[24] The systematic review by Ding *et al.*, 2017 cited here in the 2019 version of the guideline was replaced by a more recent systematic review.

al., 2023). A significantly higher clinical pregnancy rate was observed (RR 2.2, 95% CI 1.05–4.61, 2 RCT, 36 patients).

Recommendation

The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for predicted normal responders. [2019]	Conditional ⊕⊕◯◯

The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for low responders. [2025]	Conditional ⊕⊕◯◯

Justification

Available evidence has been rated of low quality. Current evidence in the form of RCT performed in normal responders have also failed to demonstrate a clear benefit of dual trigger and suffer from methodological inconsistencies, including heterogeneous inclusion criteria, inconsistent outcome definitions, and high risk of bias (Keskin et al., 2021; Eftekhari et al., 2017; Singh et al., 2022).

Evidence in low responders is very poor. The evidence comes from three very small RCT reporting conflicting results.

Regarding patients with history of low fertilization rate or high number of immature oocytes, the existing literature is limited by its observational nature. In addition, large differences are observed in the definition of low maturity rate, low fertilization rate, dose of hCG administered and most importantly lack of LBR and OHSS rate as an outcome. The dual trigger in this subgroup of patients, cannot be recommended until data on its efficacy and safety from RCTs are available.

Dual triggering for (predicted) high responder is discussed further in the guideline (chapter 19).

DOUBLE TRIGGER

Evidence

In an RCT, women with a normal response to ovarian stimulation and low oocyte maturation rate were randomised to receive either double trigger (40 and 36 hours before oocyte pick-up) or hCG only for final oocyte maturation (Yan et al., 2023). Cumulative live birth rate was significantly higher after double trigger compared to hCG only for final oocyte maturation (66.7% (24/36) vs. 36.0% (9/25)). Comparing double trigger to hCG for final oocyte maturation in women having fresh embryo transfer, no significant difference was observed for live birth rate (50% (2/4) vs. 36.4% (4/11)).

In an RCT, poor responder patients were randomised to receive either double trigger, GnRH agonist trigger with hCG bolus on day of oocyte pick-up or hCG trigger for final oocyte maturation (Haas et al., 2019). There was no significant difference in ongoing pregnancy (18.2% (2/11) vs. 0 vs. 9.1% (1/11)) or

number of MII oocytes retrieved (1.8 ± 1.4 vs. 2.1 ± 1.6 vs. 1.4 ± 1.5) between double trigger, GnRH agonist trigger or hCG trigger for final oocyte maturation.

Conclusion

There is too limited evidence to draw conclusions on the use of double trigger for final oocyte maturation for IVF/ICSI.

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18. Luteal phase support (LPS)

PICO Question: What is the efficacy and safety of luteal support protocols?

18.1 Progesterone

Evidence

An RCT compared intramuscular natural progesterone to placebo/no treatment for luteal phase support (LPS) in 156 women (Abate et al., 1999). Significantly higher live birth rates were reported with natural progesterone compared to placebo/no treatment (OR 4.21, 95% CI 0.93-19.18). Another RCT compared vaginal progesterone to placebo/no treatment for LPS in 56 women (Hurd et al., 1996). Significantly higher ongoing pregnancy rates were reported with vaginal progesterone compared to placebo/no treatment (OR 3.85, 95% CI 0.40-36.82).

Dosing

The Cochrane meta-analysis also investigated the dosage of vaginal progesterone. Five studies compared a low dose (≤100 mg) with a high dose (≥100 mg) and reported no difference in live birth/ongoing pregnancy rate (5 RCT, OR 0.97, 95% CI 0.84-1.11, 3720 women) (van der Linden et al., 2015). After the publication of the Cochrane review, a small pilot study was conducted including 146 women, investigating the effect of increasing the progesterone dosage in the mid-luteal phase in patients with progesterone levels below 15 ng/mL. There was no significant difference in live birth rate with increased progesterone dosage compared to original dosage (25% (9/36) vs. 17.1% (6/35)) (Aslih et al., 2017). Another small RCT including 111 women compared 600 mg vaginal progesterone (capsules) with 90 mg vaginal progesterone (gel) and reported no difference in live birth rate (52.8% (28/53) vs. 42.6% (20/47)) (Michnova et al., 2017).

Administration route

Several studies compared the efficacy of different administration routes for progesterone as LPS. An IPD meta-analysis compared the subcutaneous with the vaginal route (2 RCT, 1435 women) (Doblinger et al., 2016). Live birth rate was 35.3% (252/714) with subcutaneous progesterone vs. 37.6% (271/721) with vaginal progesterone (risk difference -0.02, 95% CI -0.07 to 0.03). There was no difference in incidence of OHSS between both groups (27/714 vs. 26/721; OR 1.04, 95% CI 0.60-1.81) (Doblinger et al., 2016).

Two newer RCTs also compared the efficacy of the subcutaneous and vaginal administration of progesterone for LPS (Moini et al., 2022, Salehpour et al., 2021). In the RCT by Moini *et al*., patients undergoing their first IVF cycle were randomised to receive either subcutaneous (n=40) or vaginal progesterone (n=40) (Moini et al., 2022). The clinical pregnancy rate was significantly higher with the use of subcutaneous progesterone compared to vaginal (57.5% (23/40) vs. 32.5% (13/40)). In the RCT by Salehpour *et al*., patients undergoing ICSI were randomised to receive either subcutaneous (n=100) or vaginal progesterone (n=100) (Salehpour et al., 2021). No significant difference in ongoing pregnancy rate was reported comparing subcutaneous with vaginal progesterone (37.1% (36/97) vs. 36% (36/100)).

The Cochrane meta-analysis investigated vaginal/rectal compared to the oral route and reported no difference between groups for live birth/ongoing pregnancy rate (4 RCT, OR 1.19, 95% CI 0.83-1.69, 857

women) (van der Linden et al., 2015). In a more recent RCT, infertile women were randomised on the day of final oocyte maturation trigger to receive either 400 mg/day oral micronised progesterone (n=430), 600 mg/day oral micronised progesterone (n=440) or vaginal progesterone (90 mg/day, n=440) (Niu et al., 2023). Comparing oral micronised progesterone at a dose of 400 or 600 mg/day with vaginal progesterone for LPS, no significant difference was observed for live birth rate (33.5% (144/430 vs. 29.8% (131/440) vs. 35.5% (156/440). The number of adverse events was similar in the three groups: 56 (13.0%) in the oral micronised progesterone 400 mg/day group, 60 (13.6%) in the oral micronized progesterone 600 mg/day group and 40 (9.1%) in the vaginal progesterone group.

The Cochrane meta-analysis also investigated the vaginal/rectal compared to the intramuscular route and reported no difference in live birth/ongoing pregnancy rate (7 RCT, OR 1.37, 95% CI 0.94 to 1.99, 2039 women) (van der Linden et al., 2015). A more recent RCT including 400 women also investigated the intramuscular compared to vaginal route and reported no difference in clinical pregnancy rate (26.5% (53/200) vs. 26.5% (53/200)) (Zargar et al., 2016). One very small RCT including 40 women investigated the intramuscular compared to the oral route and reported no difference in live birth rate (OR 0.71, 95% CI 0.14-3.66) (Iwase et al., 2008, van der Linden et al., 2015).

Timing

Six RCTs investigated the timing of LPS initiation (Baruffi et al., 2003, Fanchin et al., 2001, Gao et al., 2018, Mochtar et al., 2006, Sohn et al., 1999, Williams et al., 2001). One RCT compared starting LPS with progesterone on the day of oocyte retrieval with the day after oocyte retrieval in 233 women and reported no significant difference in live birth rate (46.6% (48/103) vs. 45.7% (43/94)) (Gao et al., 2018). Three RCTs compared starting LPS with progesterone on the evening of oocyte retrieval with starting on the evening of embryo transfer in respectively 103, 84 and 255 women and reported no significant difference in clinical pregnancy rate (respectively 27.4% vs. 28.8%; 42% vs. 29%; 28.1% (36/128) vs. 29.1% (37/127)) (Baruffi et al., 2003, Fanchin et al., 2001, Mochtar et al., 2006). Only one study reported live birth rate and found no significant difference between groups (21.1% (27/128) vs. 20.5% (26/127); RR 0.97, 95% CI 0.60-1.56) (Mochtar et al., 2006). One newer RCT compared starting LPS with progesterone on the day of oocyte retrieval (n=86) with the day of embryo transfer (n=85) (Ghanem et al., 2021). No significant difference was observed in ongoing pregnancy rate when LPS was started on the day of oocyte retrieval or embryo transfer (38.3% (33/86) vs. 44.7% (38/85)). Two RCTs (respectively 314 cycles and 385 women) compared starting LPS with progesterone before oocyte retrieval (respectively 12h before oocyte retrieval and at the evening of hCG trigger) with starting LPS after oocyte retrieval (Mochtar et al., 2006, Sohn et al., 1999). Mochtar *et al*. reported no significant difference in live birth (20% (26/130) vs. 21.1% (27/128); RR 0.94, 95% CI 0.58-1.52) or clinical pregnancy rate (23.1% (30/130) vs. 28.1% (36/128); RR 0.82, 95% CI 0.54-1.24) between groups (Mochtar et al., 2006). However, Sohn *et al*. found a significantly lower clinical pregnancy rate when LPS was started before oocyte retrieval compared to after (12.9% vs. 24.6%) (Sohn et al., 1999). One small RCT including 126 women compared starting LPS with progesterone on day 3 or day 6 after oocyte retrieval and found a significantly lower clinical pregnancy rate when LPS was started on day 6 compared to day 3 (44.8% vs. 61.0%) (Williams et al., 2001).

A systematic review and meta-analysis[25] including 7 RCTs compared early progesterone LPS cessation (at the 11th or 14th day post embryo transfer after a positive hCG test) with continuing progesterone

[25] The meta-analysis by Liu *et al.*, 2012 cited here in the previous version of the guideline was replaced by an updated meta-analysis.

until week 6/7 or 10 (Watters et al., 2020). No significant difference was found for the probability of the pregnancy continuing to a live birth when comparing early or late cessation of LPS (RR 0.94, 95% CI 0.84-1.00, 3 RCT, 830 participants).

Recommendations

Progesterone is recommended for luteal phase support after IVF/ICSI. [2019]	Strong ⊕◯◯◯
Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used. [2019]	GPP
The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 mg once daily for intramuscular progesterone 25 mg once daily for subcutaneous 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. [2019]	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. [2019]	GPP
Progesterone support should be administered until at least the day of the pregnancy test. [2019]	GPP

Justification

There are only two, very old RCTs comparing the use of natural progesterone to placebo/no treatment for LPS. Still, progesterone is recommended for luteal phase support for IVF/ICSI. Despite that the RCTs comparing use of natural progesterone to placebo/no treatment are scarce and old, the evidence

clearly supports the use of natural progesterone in the luteal phase. Very likely there are no future RCTs planned to challenge or confirm the existing evidence that progestins are crucial for the LPS.

Start of luteal support has not been studied properly. More studies are necessary to investigate the need of luteal support and the correct timing to support endogenous progesterone levels. Until studies have been performed, luteal support should be provided in the window between the evening of the day of oocyte retrieval and D3 post oocyte retrieval.

A meta-analysis showed no significant difference in the probability of a pregnancy progressing to a live birth between early and late cessation of progesterone support. However, the evidence investigating early cessation is not strong, with only 3 RCTs and 830 women for the outcome of live birth. In addition, early cessation contradicts the advice in the SPC's. Furthermore, two RCTs included in the meta-analysis reported on an increased incidence of vaginal bleeding with early cessation of progesterone for LPS, although this did not reach statistical significance (Aboulghar et al., 2008, Kohls et al., 2012).

With the current evidence available, no major differences in efficacy have been found comparing the different administration routes of progesterone or duration of progesterone LPS.

Current RCT on oral micronised progesterone showed non-inferiority to vaginal micronised progesterone (Niu et al., 2023). Despite these promising results, more data are necessary to be able to formulate a recommendation. Long-term offspring health studies are currently lacking.

18.2 Dydrogesterone

Evidence

Daily dosages of 30 mg dydrogesterone are most frequently used for LPS.

An IPD meta-analysis[26], including 2 RCTs, compared the use of dydrogesterone to vaginal micronised progesterone for LPS after IVF (Griesinger et al., 2020). Meta-analysis of the two RCTs with available IPD comparing dydrogesterone and vaginal micronised progesterone for LPS showed a significant higher live birth rate (OR 1.28; 95% CI 1.04-1.57, 2 RCT, 2065 women) and ongoing pregnancy rate (OR 1.32; 95% CI 1.08-1.61, 2 RCT, 2065 women) in favour of dydrogesterone. The same systematic review included a meta-analysis of the aggregate data of all eligible studies (9 RCT) and found no significant difference for live birth rate (OR 1.14; 95% CI 0.99-1.32, 5 RCT, 4470 women) or ongoing pregnancy rate (OR 1.13; 95% CI 1.00-1.28, 9 RCT, 6312 women).

A small RCT including 105 women compared the use of oral dydrogesterone with placebo for LPS and found no statistical difference in clinical pregnancy rate (29.6% (16/54) vs. 27.4% (14/51)) (Kupferminc et al., 1990).

[26] The meta-analysis by Barbosa *et al.*, 2018 cited here in the previous version of the guideline has been replaced by an updated meta-analysis. The RCT by Griesinger *et al.*, 2018 is included in the new meta-analysis and therefore no longer mentioned separately.

Recommendations

Dydrogesterone is probably recommended for luteal phase support. [2019]	Conditional ⊕⊕⊕◯

There are reports on a relation between dydrogesterone exposure and the occurrence of congenital malformations. These observed relations cannot be translated into a conclusion on causality, and therefore are considered as potential associations.

Justification

When compared to progesterone, oral dydrogesterone has similar live/birth ongoing pregnancy rate.

An older meta-analysis reported on patient dissatisfaction, including 3 RCTs, where the oral administration route was preferred over the vaginal route of progesterone in 2/3 RCTs (women in the 3rd RCT showed no difference in dissatisfaction) (Barbosa et al., 2018).

As dydrogesterone is a synthetic, orally-active progestogen, metabolised into 20-dihydrodydrogesterone, and different in structure from natural progesterone, safety for the offspring is of key importance. Evidence from the two RCTs by Tournaye *et al.* and Griesinger *et al.* reported no difference in the rate of congenital anomalies as compared to natural progesterone (Griesinger et al., 2018, Tournaye et al., 2017). A recent systematic review and meta-analysis investigated the risk of congenital malformations with dydrogesterone use in the first trimester (Katalinic et al., 2024). Six RCTs were included in the meta-analysis, 3 on threatened miscarriage (n=358, ITT) one on RPL (n=98, ITT) and two on LPS by Tournaye *et al.* and Griesinger et al. mentioned before (n= 966, ITT). They reported that the risk ratio for congenital malformations with the use of dydrogesterone was 0.92 (95% CI 0.55-1.55, 6 RCT, 1512 women) compared to placebo, no treatment or other interventions (Katalinic et al., 2024), so that offspring safety does not seem jeopardised.

However, the complete safety profile of a drug can be described only after its marketing approval, therefore, surveillance systems are needed, and suspected ADRs are now collected in very large databases (Montastruc et al., 2011). A recent case-non case study using the WHO global safety database reported that a significant disproportionate (higher than expected) reporting of birth defects was found with dydrogesterone when compared to any other drug in the study cohort, including natural progesterone (reporting OR (ROR) 5.4, 95% CI 3.9–7.5) and to any other ART drug (ROR 6.0, 95% CI, 4.2–8.5) (Henry et al., 2025). All disproportionality analysis in a pharmacovigilance database requires a clear pharmacodynamic hypothesis established on basic properties of drugs (Montastruc et al., 2011). Therefore, the findings by Henry et al. represents a pharmacovigilance signal which needs to be investigated by future prospective studies. The China maternal drug exposure birth cohort (DEBC) (Li et al., 2024) includes 112,986 pregnant women with a drug exposure rate of 30.70%, of which dydrogesterone and progesterone have the highest exposure rates with 11.97% and 10.82%, respectively. Compared to no exposure, dydrogesterone exposure during the first trimester was correlated with higher incidence of birth defects (adjusted RR 1.13, 95% CI 1.06-1.21). Compared to non-exposure, first trimester use of natural progesterone was not associated with an increased incidence of birth defects (aRR 1.05, 95% CI 0.97-1.13). These analyses were corrected for maternal age and first trimester maternal disease needing treatment. It needs to be pointed out here that these observed relations cannot be translated into a conclusion on causality, and therefore are considered as potential associations.

The final recommendation was formulated as conditional, reflecting concerns about potential safety signals from recent pharmacovigilance and a birth cohort data. Within the GDG, most members supported a conditional recommendation on dydrogesterone, but a minority disagreed.

18.3 Oestradiol supplementation

Evidence

The Cochrane meta-analysis, mentioned before, reported no difference in live birth/ongoing pregnancy rate (9 RCT, OR 1.12, 95% CI 0.91-1.38, 1651 women) or OHSS (2 RCT, OR 0.58, 95% CI 0.20-1.68, 461 women) between progesterone with oestradiol supplementation and progesterone alone (van der Linden et al., 2015). An RCT, more recent than the meta-analysis, including 220 women comparing progesterone and progesterone with oestradiol for LPS reported no significant difference in ongoing pregnancy rate (32.7% (36/110) vs. 36.3% (40/110)) (Ismail Madkour et al., 2016).

In contrast, a RCT not included in the meta-analysis investigated the effect of adding oestradiol to a high dose of progesterone (200 mg vaginal capsules 3x/day + 100 mg intramuscular daily) for LPS in 240 women and reported a significant higher clinical pregnancy rate with oestradiol supplementation in women undergoing the long GnRH agonist and short flexible GnRH antagonist protocol (43.3% vs. 35% and 60% vs. 36.6% resp.), but not with the short GnRH agonist protocol (43.3% vs. 40%) (Gizzo et al., 2014).

Two RCTs compared different dosages of oestradiol in addition to progesterone for LPS (Kutlusoy et al., 2014, Tonguc et al., 2011). Tonguc *et al.* compared vaginal progesterone with 3 different dosages of oestradiol (2-4-6 mg) in 285 women and found no difference in clinical pregnancy rate between groups (31.6% (30/95) vs. 40% (38/95) vs. 32% (31/95) resp.) (Tonguc et al., 2011). Kutlusoy *et al.* compared vaginal progesterone with 2 mg oestradiol and 6 mg oestradiol in 62 women and found no significant difference in live birth rate between dosages (37% (10/27) vs. 22.9% (8/35)) (Kutlusoy et al., 2014).

Recommendation

The addition of oestradiol to progesterone for luteal phase support is probably not recommended.	Conditional ⊕⊕◯◯

Justification

The data suggests that oestradiol is not recommended for LPS, since it does not improve efficacy in terms of live birth/ongoing pregnancy rate, or safety in terms of OHSS.

18.4 Human chorionic gonadotrophin (hCG)

Evidence

The Cochrane meta-analysis, mentioned before, found a higher live birth/ongoing pregnancy rate with hCG for LPS compared to placebo/no treatment (3 RCT, OR 1.76, 95% CI 1.08-2.86, 527 women) (van der Linden et al., 2015). However, the OHSS rate was increased with hCG for LPS (1 RCT, OR 4.28, 95% CI 1.91-9.60, 387 women) (Belaisch-Allart et al., 1990, van der Linden et al., 2015).

When compared to progesterone, hCG for LPS or supplementation of progesterone with hCG did not have a beneficial effect on live birth/ongoing pregnancy rate (5 RCT, OR 0.95, 95% CI 0.65-1.38, 833 women). Furthermore, progesterone was associated with lower rates of OHSS rates than hCG with or without progesterone (5 RCT, OR 0.46, 95% CI 0.30-0.71, 1293 women) (van der Linden et al., 2015).

Two pilot RCTs, one in women experiencing a normal response to ovarian stimulation with low risk of OHSS (≤13 follicles) and the second in women experiencing a normal response at risk of OHSS (14-25 follicles). In both pilot studies, the study group received GnRH agonist for final oocyte maturation trigger, combined with two boluses of hCG after oocyte retrieval and on day 4 after oocyte retrieval (n=50 in RCT 1 and n=46 in RCT 2). The control group in both pilot studies received hCG for final oocyte maturation trigger and vaginal progesterone (3x daily) for luteal support (n=54 in RCT 1 and n=52 in RCT 2) (Humaidan et al., 2021). In women at low risk of OHSS, no cases of OHSS were reported. When comparing hCG and progesterone for LPS, there was no significant difference in live birth rate (40% (20/50 vs. 46% (25/54)) or ongoing pregnancy rate (44% (22/50) vs. 46% (25/54)). In women at risk of OHSS, two cases of OHSS were reported in the study group, compared to 4 in the control group (not statistically significant). No significant difference was observed with hCG compared to progesterone for LPS for live birth rate (51% (25/49) vs. 58% (30/52)), ongoing pregnancy (51% (25/49) vs. 60% (30/52)) or number of MII oocytes retrieved (12.3±4.4 vs. 12.2±4.6).

One small study including 91 women compared hCG with progesterone combined with oestradiol for LPS and found no difference in clinical pregnancy rate (RR 0.99, 95% CI 0.50-1.92) (Smitz et al., 1988).

Recommendations

In hCG triggered ovarian stimulation cycles, hCG as luteal phase support in standard dosages of 1500 IU is not recommended. [updated]	Strong	⊕⊕◯◯

Justification

hCG is equal to progesterone protocols regarding efficacy. However, hCG increased the OHSS risk, specifically in high responders and with the dosages historically used (1500 IU).

Studies comparing hCG and progesterone for luteal support have not been stratified according to ovarian response.

18.5 GnRH agonist

18.5.1 Single GnRH agonist bolus supplementation

Evidence

Most of the studies administered a single bolus of GnRH agonist for LPS on day 6 after oocyte pick-up at a dose of 0.1 mg for triptorelin and 1 mg for leuprolide.

A systematic review[27] and meta-analysis compared the use of a bolus GnRH agonist to the control LPS protocol (Liu et al., 2022). No significant difference was found between a single-dose GnRH agonist and control for LPS for live birth rate (OR 1.29, 95% CI 0.90-1.84, 6 RCT, 644 participants).

Recommendation

A GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. [updated]	Conditional	⊕⊕◯◯

Justification

The use of GnRH agonist for LPS needs further evaluation in well-designed RCTs, available studies in the meta-analysis have been rated as of very low quality. Current evidence indicates no significant difference in live birth/pregnancy rates with GnRH agonist bolus in addition to progesterone for LPS. It does not seem to increase the risk of OHSS (Yildiz et al., 2014).

Long-term health effects in the new-born have not been studied.

18.5.2 REPEATED GNRH AGONIST

Evidence

Most of the studies administered GnRH agonist for LPS at dosages of 0.1 mg for triptorelin and 1 mg for leuprolide.

The Cochrane meta-analysis reported that multiple doses GnRH agonist added to progesterone for LPS significantly increased live birth/ongoing pregnancy rate compared to progesterone alone (5 RCT, OR 0.64, 95% CI 0.42-0.98, 1325 women) (van der Linden et al., 2015). One RCT in the meta-analysis reported OHSS and showed no difference between the groups (OR 1.00, 95% CI 0.33-3.01, 300 women) (van der Linden et al., 2015, Yildiz et al., 2014).

Recommendation

Repeated GnRH agonist injections, alone or in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. [reworded]	Conditional	⊕◯◯◯

Justification

Current evidence indicates higher live birth /pregnancy rates with GnRH agonist alone or in addition to progesterone for LPS. The evidence on safety of GnRH agonist for LPS is very limited (1 RCT), however,

[27] The meta-analysis by Van der Linden *et al.*, 2015 cited here in the previous version of the guideline was replaced by an updated meta-analysis. The RCTs by Razieh *et al.*, 2009 and Zafardoust *et al.*, 2015 are included in the new meta-analysis and therefore no longer mentioned separately.

it does not seem to increase the risk of OHSS (Yildiz et al., 2014). The evidence on GnRH agonist for LPS in GnRH antagonist cycles is also limited.

Long-term health effects in the new-born have not been studied. Until these data are available, the GDG recommends against using GnRH agonist for LPS.

18.6 LH SUPPLEMENTATION

Evidence

One small RCT including 35 women reported no difference in live birth rate (22.2% (4/18) vs. 23.5% (4/17)) or number of oocytes retrieved (11.7±1.9 vs. 13.8±1.8) between the LH supplementation group and the progesterone alone group. No cases of OHSS were reported in either group (Papanikolaou et al., 2011).

Recommendation

Addition of LH to progesterone for luteal phase support can only be used in the context of a clinical trial. [2019]	Research only

Justification

The available evidence consists of 1 very small pilot study, which has investigated the effect of adding LH to progesterone for LPS. However, the study and control group received different triggers for final oocyte maturation (rhCG compared to GnRH agonist). Therefore, no conclusions can be drawn on the effect of LH supplementation for LPS, and this intervention cannot be recommended.

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PART G: Prevention of OHSS

In previous sections, recommendations were formulated regarding the preferable protocol of ovarian stimulation for predicted high responders. In short, evidence indicates that GnRH antagonist protocol is as effective as the GnRH agonist protocol, and significantly reduces the risk of OHSS in PCOS women (Liu et al., 2023). Even though there is no specific evidence on predicted non-PCOS high responders or PCOM patients, consensus of the guideline group is that GnRH antagonist protocol should also be recommended in these patient groups (section 4A, page 48). Furthermore, evidence from one RCT indicated that in case an GnRH agonist protocol is used in high responders, a reduced gonadotropin dose may decrease the risk of OHSS (Oudshoorn et al., 2017). Progestin protocol stimulation allows the use of a GnRH agonist trigger and avoids a fresh embryo transfer. Given similar effectiveness to GnRH analogues for pituitary suppression progestin protocol can be considered a patient friendly and cost effective option for planned freeze all cycles in patients with an anticipated high response and risk of OHSS.

A reduced gonadotropin dose is probably recommended to decrease the risk of OHSS in predicted high responders. [2025]	Conditional	⊕◯◯◯

The GnRH antagonist protocol is recommended for predicted high responders. However, if GnRH agonist protocols are used, a reduced gonadotropin dose is recommended to decrease the risk of OHSS. [updated]	Strong	⊕◯◯◯

If freeze-all is planned, the use of progestin for pituitary suppression is probably equally recommended to GnRH analogues. [updated]	Conditional	⊕◯◯◯

19. Prevention of OHSS

PICO Question: Which GnRH agonist medication as a method of triggering will add to the prevention of the ovarian hyperstimulation syndrome also with regards to overall efficacy?

GnRH agonist trigger vs hCG trigger in (predicted) high responders

Evidence

GnRH agonist vs hCG 10.000 IU trigger and fresh transfer

A Cochrane meta-analysis comparing GnRH agonist trigger with hCG trigger found that GnRH agonist trigger was associated with a significantly lower risk of moderate/severe OHSS when compared with hCG among women at high risk of OHSS (3 RCT, OR 0.09, 95%CI 0.02-0.52, 212 women) (Youssef et al., 2014).

Due to technical limitations of the meta-analysis, all other outcomes were collected from individual studies. In an RCT including 28 PCO women, comparing GnRH agonist with hCG for final oocyte maturation, no significant difference was found for live birth rate (1/15 vs. 2/13) or number of oocytes retrieved (19.8 ± 2.5 vs. 19.5 ± 1.9) (Babayof et al., 2006). Similarly, in an RCT including 66 women with PCOS or previous high response, no significant difference was found in ongoing pregnancy rate (53.3% (16/30) vs. 48.3% (14/29)) or number of oocytes retrieved (20.2±9.9 vs. 18.8±10.4) between GnRH agonist and hCG for final oocyte maturation (Engmann et al., 2008). It is noted that the latter trial employed augmented luteal phase support protocols with additional oestrogen with intramuscular progesterone in the GnRH agonist triggered arm.

GnRH agonist trigger with fresh transfer vs freeze-all

An RCT including 212 women at risk of OHSS (>17 follicles of >11 mm on the day of trigger) compared GnRH agonist trigger in GnRH antagonist protocol with or without a freeze all (Santos-Ribeiro et al., 2020). While live birth rates were similar (39.4% (41/104) vs. 41.6% (42/101)), moderate-to-severe OHSS occurred only in the fresh transfer group that was given an additional single low-dose hCG on the day of the trigger (8.6% (9/105), 95% CI 3.2-13.9% vs. 0% (0/104), 95% CI 0-3.7%) (Santos-Ribeiro et al., 2020).

An RCT including 280 women at risk of OHSS (number of follicles ≥12 mm between 14 and 25 on the day of trigger) compared GnRH agonist trigger with or without freeze-all (Aflatoonian et al., 2018). There was no significant difference in live birth rate (27.3% (33/121) vs. 26.9% (32/119); OR 1.02, 0.57-1.80) or moderate OHSS (5.8% (7/121) vs. 5.9% (7/119)) between GnRH agonist trigger with freeze-all or fresh transfer. No cases of severe OHSS were reported in either group (Aflatoonian et al., 2018).

GnRH agonist vs hCG non-10.000 IU trigger and fresh transfer

One RCT including 118 patients at risk of OHSS (between 14 and 25 follicles ≥11 mm diameter on trigger day) reported no difference in OHSS between GnRH agonist trigger (0% (0/60)) compared to reduced hCG dose (3.4% (2/58)) in a GnRH antagonist protocol. No severe OHSS was reported in either group. Ongoing pregnancy rates were similar for GnRH agonist trigger (28.3% (17/60)) compared to reduced-dose hCG trigger (25.9% (15/58)) and also a similar number of oocytes was retrieved in both groups (13.7±5.9 vs. 13.5±5.7) (Humaidan et al., 2013). It is noted that augmented luteal phase support protocols with additional doses of hCG were employed in the GnRH agonist triggered arm.

Recommendation

A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS combined with a freeze-all strategy to minimise the risk of severe OHSS. [updated]	Strong ⊕◯◯◯
If a GnRH agonist protocol with hCG trigger is used in high responders, a freeze-all strategy is recommended to decrease the risk of late-onset OHSS. [updated]	GPP

Justification

Triggering final oocyte maturation with GnRH agonist significantly reduces the risk of early-onset OHSS in patients at risk of OHSS.

Limited evidence suggests that GnRH agonist trigger with fresh transfer is as efficient and safe as GnRH agonist trigger with freeze-all in patients at risk of OHSS with number of follicles ≥12 mm between 14 and 25 on the day of trigger. Modified luteal support with LH-activity (hCG or LH) may overcome the reduction in clinical pregnancy rate after GnRH agonist trigger. However, its effectiveness of OHSS prevention is reduced.

DUAL TRIGGER

Evidence

In a retrospective cohort study, dual trigger was compared to GnRH agonist for final oocyte maturation in PCOS patients undergoing ovarian stimulation for IVF/ICSI with freeze-all (Wang et al., 2024). No significant difference in live birth rate was observed when comparing dual trigger to GnRH agonist only for final oocyte maturation (56.2% (99/176) vs. 63.1% (111/176)). However, the total OHSS rate (14.8% (26/176) vs. 2.8% (5/176)) and the moderate/severe OHSS rate (11.4% (20/176) vs. 1.7% (3/176)) were significantly higher after dual trigger compared to GnRH agonist only.

In a retrospective cohort study, dual trigger with 1000 IU (n=403) or 2000 IU hCG (n=363) was compared to GnRH agonist trigger only (n=577) in high responders to ovarian stimulation having freeze-all (He et al., 2022). Comparing GnRH agonist only to both groups of dual trigger (1000 IU and 2000 IU hCG, respectively), there was no significant difference for cumulative live birth rate (74.4% (429/577) vs. 75.7% (305/403) vs. 69.7% (253/363)) or live birth rate (54.2% (302/577) vs. 54.5% (212/389) vs. 54.3% (191/352)). However, moderate to severe OHSS rate was significantly higher with dual trigger (1000 IU and 2000 IU hCG, respectively) compared to GnRH agonist trigger alone (1.5% (6/403) vs. 1.4% (5/363) vs. 0%).

Recommendation

The addition of hCG to GnRH agonist as a dual trigger for final oocyte maturation is probably not recommended for high responders. [2025]	Conditional ⊕◯◯◯

Justification

The supporting evidence comes from retrospective cohort studies. No difference in efficacy was observed with dual trigger compared to GnRH agonist trigger. However, both studies reported significantly more cases of OHSS in the dual trigger group. Because of these safety concerns, adding hCG to GnRH agonist as dual trigger cannot be recommended in high responders.

GnRH agonist trigger + freeze-all vs hCG trigger+freeze-all in (predicted) high responders

Evidence

A case-control study, including 248 women at risk of OHSS, compared GnRH agonist trigger and freeze-all to hCG trigger and freeze-all. There was no significant difference in cumulative pregnancy rate between GnRH agonist and hCG trigger with freeze-all (59.5% vs. 53.0%) (Borges et al., 2016).

Similar results were found in a retrospective cohort study including 272 women at risk of OHSS, also comparing hCG trigger and freeze-all with GnRH agonist trigger and freeze-all. There was no difference in cumulative live birth rate between GnRH agonist and hCG for final oocyte maturation and freeze-all (48.15% vs. 48.08%) (Tannus et al., 2017).

Recommendation

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. [2019]	Conditional ⊕◯◯◯

Justification

Available evidence is derived from low-quality studies in patients at risk of OHSS. However, evidence from RCTs performed in oocyte donors indicates that GnRH agonist trigger is preferable over hCG when a freeze-all strategy is applied (Acevedo et al., 2006, Galindo et al., 2009, Melo et al., 2009, Sismanoglu et al., 2009). The guideline group thinks that the data can be extrapolated to GnRH agonist trigger compared to hCG with freeze-all in both arms for patients at risk of OHSS.

GnRH agonist trigger vs coasting+hCG trigger in (predicted) high responders

Evidence

A retrospective study including 94 women at risk of OHSS reported that 10/33 women in the coasting group had cycle cancellation because of the risk of development of OHSS vs. 0/61 in the GnRH agonist trigger group. No cases of OHSS occurred in either treatment group. Ongoing pregnancy rates (49.2%

(30/61) vs. 24.2% (8/33)) and number of oocytes retrieved (26.9±9.5 vs. 17.7±9.3) were significantly higher in the GnRH agonist trigger group compared to the coasting group (DiLuigi et al., 2010).

Another retrospective study including 248 women at risk of OHSS reported more cancelled cycles in the coasting group compared to the GnRH agonist trigger with freeze-all group (19.7% (30/152) vs. 8.3% (8/96) because of poor embryo quality or risk of OHSS. The clinical pregnancy rate in the coasting group was 29.5% (36/122), which was significantly lower than the GnRH agonist trigger with freeze-all (50% (44/88)) (Herrero et al., 2011).

Recommendation

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. [2019]	GPP

Justification

The two most relevant studies were both on retrospective data, with inherent methodological and risk of bias problems. Therefore, the GDG cannot recommend coasting and hCG trigger over GnRH agonist trigger for final oocyte maturation in patients at risk of OHSS.

DOPAMINE AGONISTS

Evidence

A systematic review and meta-analysis comparing a dopamine agonist to no intervention or placebo included 10 RCTs with 1202 participants and reported significantly lower risk of moderate or severe OHSS with the use of dopamine agonists (OR 0.32, 95% CI 0.23-0.44). Live birth rates were reported in only 3 RCTs, including 362 participants, and were similar in the two groups (OR 0.96, 95% CI 0.60-1.55) (Tang et al., 2021).

A retrospective study, including 480 patients at risk of OHSS, compared GnRH agonist trigger alone, GnRH agonist trigger and a dopamine agonist from the day of trigger or oocyte retrieval for seven days, and GnRH agonist with dopamine agonist as described above in combination with daily GnRH antagonist for five days from oocyte retrieval day (Shrem et al., 2019). All embryos were frozen in the three groups. None of the patients developed severe OHSS, however, the incidence of mild or moderate OHSS was significantly higher in the GnRH agonist trigger only group than in the GnRH agonist trigger and dopamine agonist group (38% vs. 29%) and the GnRH agonist trigger, dopamine agonist and GnRH antagonist group (38% vs. 18%). The GnRH agonist trigger and dopamine agonist groups had a significantly higher risk of mild or moderate OHSS than the GnRH agonist trigger in combination with dopamine agonist and GnRH antagonist (29% vs. 18%).

Recommendation

Dopamine agonists are recommended to decrease the risk of early OHSS, particularly in patients receiving hCG for final oocyte maturation. [2025]	Strong	⊕⊕◯◯

Justification

The GDG recommends using GnRH agonist trigger combined with freeze-all for women at risk of OHSS. However, if the patient is deemed at risk of OHSS after an hCG trigger, dopamine agonist can be used as a preventive measure for early OHSS. Dopamine agonists inhibit endothelial VEGF receptors and decrease vascular permeability. However, rapid luteolysis with a GnRH agonist trigger combined with a freeze all strategy may render the addition of dopamine agonists obsolete or marginally effective with regard to clinically relevant OHSS in cycles with GnRH antagonist pituitary suppression.

PICO Question: Is the freeze-all protocol meaningful in the prevention of ovarian hyper-stimulation syndrome also with regard to efficacy?

Ovarian hyperstimulation syndrome (OHSS) is a potential life-threatening condition. It implies hospitalization frequently, with health care additional costs and patient burden. However, it may be balanced to the possible negative effects of a freeze-all policy and the decline in live birth rates, due to eliminating the fresh transfer from the treatment scheme.

Evidence

A Cochrane systematic review and meta-analysis comparing freeze-all to conventional ovarian stimulation with fresh transfer reported a significantly lower incidence of OHSS (0.8% vs. 3.7% (Peto OR 0.26, 95% CI 0.17-0.39; 6 RCTs, 4478 women)) with the freeze-all strategy compared to fresh transfer. Furthermore, they found no difference in cumulative live birth rate and pooled for all embryo stages at transfer (OR 1.08, 95% CI 0.95-1.22; 8 RCTs, 4712 women) (Zaat et al., 2021).

Recommendation

A freeze-all strategy is recommended to minimise the risk of late-onset OHSS. [updated]	Strong	⊕⊕◯◯

Prior to start of ovarian stimulation, a risk assessment for high response is advised with the purpose of applying personalised treatment choices on pituitary suppression protocol, FSH dosage, final oocyte maturation trigger and embryo transfer strategy. [updated]	GPP

Justification

The current evidence suggests that not performing a fresh embryo transfer lowers the OHSS risk for women at risk of OHSS, without completely eliminating the condition. The latter urges for follow up of haemo-concentration status even in cases with the freeze-all strategy applied.

The conditions with a high prior risk of developing the OHSS comprise:

- patients with the PCOS syndrome,
- patients with an above average ovarian reserve status
- patients exhibiting a high ovarian response as indicated by follicle number at ultrasound, high oestradiol levels, or high number of oocytes obtained

Applying the freeze-all strategy implies the presence of a high-quality cryopreservation program.

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Glossary

Ovarian hyperstimulation syndrome (OHSS)	An exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It may be classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, hemodynamic and metabolic complications.
Ovarian stimulation (OS)	Pharmacological treatment with the intention of inducing the development of ovarian follicles. It can be used for two purposes: 1) for timed intercourse or insemination; 2) in ART, to obtain multiple oocytes at follicular aspiration.
Low ovarian responder in assisted reproductive technology	A woman treated with ovarian stimulation for ART, in which at least two of the following features are present: (1) Advanced maternal age (≥40 years); (2) A previous low ovarian response (≤3 oocytes with a conventional stimulation protocol aimed at obtaining more than three oocytes); and, (3) An abnormal ovarian reserve test (i.e. antral follicle count 5–7 follicles or anti-Mullerian hormone 0.5–1.1 ng/ml (Bologna criteria); or other reference values obtained from a standardized reference population.)
Low ovarian response to ovarian stimulation	A condition in which fewer than four follicles and/or oocytes are developed/obtained following ovarian stimulation with the intention of obtaining more follicles and oocytes.
Mild ovarian stimulation	A protocol in which the ovaries are stimulated with gonadotropins, and/or other pharmacological compounds, with the intention of limiting the number of oocytes following stimulation for IVF.
Modified natural cycle	A procedure in which one or more oocytes are collected from the ovaries during a spontaneous menstrual cycle. Pharmacological compounds are administered with the sole purpose of blocking the spontaneous LH surge and/or inducing final oocyte maturation

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Annexes

Annex 1: Guideline development group

This guideline was developed by the ESHRE Reproductive Endocrinology Guideline Development Group (GDG). The GDG included gynaecologists with expertise in reproductive medicine and ovarian stimulation. We aimed for an equal distribution in gender, region and expertise.

Chair of the GDG

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Methodological support

Nathalie Le Clef	European Society of Human Reproduction and Embryology (Belgium)

DECLARATIONS OF INTEREST

All members of the guideline development group were asked to declare possible conflicts of interest by means of the disclosure forms (see *ESHRE Manual for Guideline Development*).

	Conflicts of interest
Frank Broekmans	Research grants from Merck, Ferring, Besins Consulting fees from Ferring, Merck, Besins, Abbott Speaker's fees from Merck, Besins, Ferring
Nikolaos P. Polyzos	Research grants from Besins, Ferring, Merck, Organon, Roche Diagnostics and Theramex Consulting fees from Besins, Ferring, IBSA, Merck, Organon, and Abbott Speaker's fees from Besins, Ferring, Gedeon-Richter, IBSA, Merck, Organon and Theramex
Antonio La Marca	Research grants from Merck, Ferring, IBSA, Roche, Organon, Theramex, Beckman Coulter and Gedeon-Richter Consulting fees from Merck, Ferring, IBSA, Roche, Organon, Theramex, Beckman Coulter and Gedeon-Richter Speaker's fees from Merck, Ferring, IBSA, Roche, Organon, Theramex, Beckman Coulter and Gedeon-Richter
Georg Griesinger	Consulting fees from Organon, Ferring, Merck, Gedeon-Richter, Theramex, Abbott, ReproNovo, Igyxos, OxoLife, Philipps, ReprodWissen, PregLem, Guerbet, Roche, IBSA, and Besins. Speaker's fees from Organon, Ferring, Merck, Gedeon-Richter, Theramex, Abbott, ReproNovo, Igyxos, OxoLife, Philipps, ReprodWissen, PregLem, Guerbet, Roche, IBSA, and Besins. Research grants from Besin, Merck, Abbott, Ferring, Theramex.
Ernesto Bosch	Research grants from Gedeon-Richter Consulting fees from MSD, Ferring, Abbot, Gedeon-Richter, Merck, Roche Speaker's fees from MSD, Ferring, Abbot, Gedeon-Richter, Merck, Roche Ownership interest from IVI-RMS Valencia
Baris Ata	Speaker's fees from Gedeon-Richter, Ferring, IBSA, Intas, Merck, Organon. Consulting fees from Merck, Organon, Oxolife.
Janos Urbancsek	None declared.
Nathalie Massin	Research grants from IBSA, Organon Consulting fees from Organon, Merck, GE, Ferring Speaker's fees from Merck, Gedeon-Richter, Theramex
Töyli Mira	None declared.
Michael Grynberg	Speaker's fees from Merck Serono, Ferring, Gedeon Richter
Sesh Kamal Sunkara	Research grant from Ferring Consulting fees from Merck Speaker's fees from Merck and Ferring
Simone Broer	None declared.
George Lainas	Consulting and speaker's fees from Organon, Ferring, Merck, Gedeon-Richter, Cook, Vianex.
Estratios Kolibianakis	Travel/hotel expenses from Ferring, SERONO, Vianex

	Chair of the Greek Society of Fertility and Sterility
Michal Kunicki	Speaker's fees from Ferring
Tanya Timeva	Speaker's fees from Merck, Organon, MSD
Nathalie Le Clef	None declared.

Annex 2: Abbreviations

AFC	Antral follicle count
AMH	Anti-Müllerian hormone
ART	Assisted reproductive technology
BMI	Body mass index
CC	Clomiphene citrate
CI	Confidence interval
COC	Cumulus-oocyte complex
COCP	Combined oral contraceptive pill
DHEA	Dehydroepiandrosterone
Duostim	Double stimulation, ovarian stimulation during the follicular and luteal phase of the same cycle
EFORT	Exogenous follicle stimulating hormone ovarian reserve test
EMT	Endometrial thickness
FSH	Follicle stimulating hormone
GDG	Guideline development group
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
GPP	Good practice point
hCG	Human chorionic gonadotrophin
hMG	Human menopausal gonadotropin
hp-FSH	Highly purified follicle stimulating hormone
ICSI	Intracytoplasmic sperm injection
IPD	Individual patient data
IU	International unit
IUI	Intra-uterine insemination
IVF	In vitro fertilization
LBR	Live birth rate
LH	Luteinizing hormone
LPS	Luteal phase support
LR	Likelihood ratio
MD	Mean difference
MNC	Modified natural cycle
MPA	Medroxy progesterone acetate
OHSS	Ovarian hyperstimulation syndrome
OPU	Oocyte pick-up
OR	Odds ratio
OS	Ovarian stimulation
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
p-FSH	Purified follicle stimulating hormone
POI	Premature ovarian insufficiency
PR	Pregnancy rate
RCT	Randomized controlled trial
r-hFSH	Recombinant human follicle stimulating hormone
rLH	Recombinant luteinizing hormone
ROC-AUC	Receiver operating characteristic – area under the curve
RR	Relative risk/risk ratio
SMD	Standardized mean difference
WMD	Weighted mean difference

Annex 3: Recommendations for research in OS for IVF/ICSI

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, the GDG recommends that future research, where possible in well-designed RCTs, should focus on these research gaps.

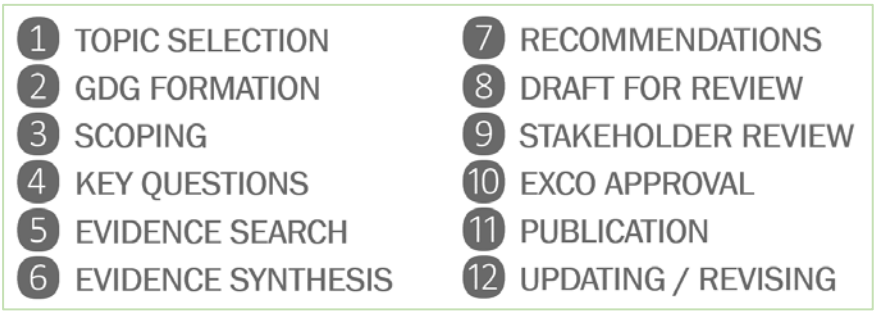
Considered are:

- Implementation studies on FSH dosing assignment/choice tools to rationally optimise safety profiles and live birth rates.
- Gonadotropin 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).
- The effect on live birth rates of deferring embryo transfer in situations with elevated Progesterone on the day of the trigger, compared to standard scheduling the fresh transfer in day 5 transfer programmes.
- Changing from r-hFSH stimulation to hMG stimulation or vice versa in cases with a high rate of immature oocytes (M1 and/or GV) after a standard stimulation phase and 10.000 IU hCG trigger: will it affect the immature oocyte rate and live birth rate?
- Comparing the use of the PPOS scheme in predicted high responders to the use of a standard antagonist stimulation scheme with FSH dosage adjustment and fresh transfer,, with respect to live birth, safety for the female and safety for the offspring and time to pregnancy
- The effect of applying a FSH dose adaptation on day 5-6 of the stimulation versus continuing the same FSH dose from the start, provided that the FSH dose has been chosen based on prior identification of the predicted ovarian response, on FSH consumption and live birth prospects.

Annex 4: Methodology

GUIDELINE DEVELOPMENT

European Society of Human Reproduction and Embryology (ESHRE) guidelines are developed based on the Manual for ESHRE guideline development (Vermeulen et al., 2020), which can be consulted at the ESHRE website (www.eshre.eu/guidelines). The principal aim of this manual is to provide stepwise advice on ESHRE guideline development for members of ESHRE guideline development groups. The manual describes a 12-step procedure for writing clinical management guidelines by the guideline development group, supported by the ESHRE methodological expert:



The two versions of this guideline (2019 and 2025) were developed and funded by ESHRE, which covered expenses associated with the guideline meetings (travel, hotel and catering expenses) associated with the literature searches (library costs, costs associated with the retrieval of papers) and with the implementation of the guideline (printing, publication costs). Except for reimbursement of their travel expenses, GDG members did not receive any payment for their participation in the guideline development process.

For the 2019 version of the guideline, the scope of the guideline and first version of the key questions were drafted by the coordinator and deputies of the ESHRE Special Interest Group Reproductive Endocrinology. A call was launched for experts in the field interested in joining the guideline development group. All applications were reviewed, and experts were selected based on expertise and geographical location. We strived towards a balance in gender and location within Europe. A meeting of the guideline development group was organized to discuss the key questions and redefine them through the PICO process (patients – interventions – comparison – outcome). This resulted in a final list of 18 key questions. Based on the defined key words, literature searches were performed by the methodological expert (Dr. N. Le Clef). Key words were sorted to importance and used for searches in PUBMED/MEDLINE and the Cochrane library. We searched the databases from inception up to 8 November 2018. For the 2025 update of the guideline, all guideline group members of the 2019 were contacted to be part of the guideline development group, one member declined and was replaced. The key questions of the 2019 version were reviewed and refined, and new interventions were added were relevant. An update of the literature searches was performed by the methodological expert (Dr. N. Le Clef). We searched the databases for literature published between 1 November 2018 and 2 February 2025.

Literature searches were performed as an iterative process. In a first step, systematic reviews and meta-analyses were collected. If no results were found, the search was extended to randomized controlled

trials, and further to cohort studies and case reports, following the hierarchy of the levels of evidence. Reference were selected or excluded by the methodological expert and expert GDG member based on title and abstract and knowledge of the existing literature. If necessary, additional searches were performed in order to get the final list of papers. For interventional questions, focus was on prospective (randomized) controlled studies. . It is not within ESHRE's remit to conduct a formal investigation or to draw formal conclusions regarding the misconduct of an individual or group of individuals or to determine whether a published article should be retracted. However, papers that are withdrawn, have a published editorial note of concern or a published expression of concern have been excluded from the guideline. In future revision or update of the guideline, the GDG will actively verify the status of all the referenced studies.

The quality of the selected papers was assessed by means of the quality assessment checklist, defined in the ESHRE guideline manual. Furthermore, the evidence was collected and summarized in an evidence table according to GIN format (http://www.g-i-n.net/activities/etwg). The quality assessment and evidence tables were constructed by the expert GDG members.

Summary of findings tables (Annex 6) were prepared following the GRADE approach for randomized controlled intervention studies which reported the critical outcomes, i.e. cumulative live birth rate, live birth rate and OHSS rate. Where available, summary of findings tables were based on existing up-to-date well-executed systematic reviews, if necessary supplemented with additional recent RCTs. When there was no recent valid systematic review available, we systematically searched for relevant studies, as described above, with focus on prospective (randomized) studies.

GDG meetings were organized to discuss the draft recommendations and the supporting evidence and to reach consensus on the final formulation of the recommendations. In a final step, all evidence and recommendations were combined in the ESHRE guideline: “Ovarian stimulation for IVF/ICSI”.

FORMULATION OF RECOMMENDATIONS

We labelled the recommendations as either ‘‘strong’’ or ‘‘conditional’’ according to the GRADE approach. We used the words ‘‘we recommend’’ for strong recommendations and ‘‘we probably recommend’’ for conditional recommendations. Suggested interpretation of strong and conditional recommendations by patients, clinicians and health care policy makers is as follows:

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 Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Recognise 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 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	Policy making will require substantial debate and involvement of various stakeholders

For each recommendation it is mentioned whether it is strong or conditional and what the quality of the supporting evidence was. In the justification section, more data are provided on the considerations taken into account when formulating the recommendations: balance between desirable and undesirable effects, certainty of the evidence of effects, certainty in how people value the outcome, acceptability and feasibility of the intervention. Impact on health equity and resource impact were only discussed where relevant.

Strategy for review of the Guideline draft

After finalization of the guideline draft, the review process was initiated. The draft guideline was published on the ESHRE website, accompanied by the reviewers' comments form and a short explanation of the review process. The guideline was open for review between 6 May and 16 June 2025.

To notify interested clinicians, we sent out an invitation to review the guideline by email to all members of ESHRE. In addition, selected reviewers were invited personally by email.

All reviewers are listed in Annex 5. The Reviewer comments processing report, including further information on the review and a list of all comments per reviewer with the response formulated by the GDG will be published on the ESHRE website.

Guideline Implementation strategy

The standard dissemination procedure for all ESHRE guidelines comprises publishing and announcement.

Each guideline is published on the ESHRE Website and in Human Reproduction Open. The announcement procedure includes a news item in "Focus on Reproduction", a newsflash on the ESHRE website homepage and a short presentation at the ESHRE Annual meeting. All participants in the annual ESHRE meeting will be informed about the development and release of new guidelines; all related national societies and patient organizations are informed about the guideline release. They are asked to encourage local implementation by, for instance, translations or condensed versions, but they are also offered a website link to the original document.

Patient versions of the guideline will be developed by a subgroup of the GDG together with patient representatives. The patient version is a translation of the recommendations in everyday language, with emphasis on questions important to patients. It aims to help patients understand the guideline's recommendations and facilitates clinical decision-making.

To further enhance implementation of the guideline, the members of the GDG, as experts in the field, will be asked to select recommendations for which they believe implementation will be difficult and make suggestions for tailor-made implementation interventions (e.g. option grids, flow-charts, additional recommendations, addition of graphic/visual material to the guideline).

Schedule for updating the guideline

The current guideline will be considered for revision in 2029 (four years after publication). An intermediate search for new evidence will be performed two years after publication, which will inform the GDG of the necessity of an update.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found at www.eshre.eu/guidelines.

For more details on the methodology of ESHRE guidelines, visit www.eshre.eu/guidelines

Annex 5: Stakeholder consultation

As mentioned in the methodology, the guideline draft was open for review for 6 weeks, between 6 May and 16 June 2025. All reviewers, their comments and the reply of the guideline development group are summarized in the review report, which is published on the ESHRE website as supporting documentation to the guideline. The list of representatives of professional organization, and of individual experts that provided comments to the guideline are summarized below.

Representatives of professional organisations

Organisation	Country	Representative
Gulsara Z. Eshimbetova	Uzbekistan	Association of reproductive medicine of Uzbekistan
Galina Grebennikova	Kazakhstan	Kazakhstan Association on Sexual and Reproductive Health (KMPA)
Assel Jaimbetova	Kazakhstan	Institute of Reproductive Health Almaty Kazakhstan
Monu Pattanayak	India	Shanti Memorial Hospital
Ulughbek Jabborov	Uzbekistan	Republican Perinatal Centre
Liudmyla Hutsikava	Republic of Belarus	Department of Obstetrics and Gynecology of Grodno State Medical University
Zaytuna Khamidullina	Kazakhstan	Federation of obstetrician-gynecologists of Astana city
Pavika Lal	India	Ganesh Shankar Vidyarthi Medical College
Hisham A. Arab	Saudi Arabia	Saudi Obstetrics and Gynecology Society
Farah Gari	Algeria	Department of gynecology and obstetrics, university hospital of Blida
Zeev Shoham **Ariel Weissman** **Raoul Orvieto**	Israel	IVF-Worldwide
Johannes Ott	Austria	Austrian association of Gynecology and Obstetrics (Working Group for Gynecologic Endocrinology and Reproductive Medicine
Ariane Germeyer **Martin Birkhäuser** **Bettina Böttcher** **Bruno Imthurn** **Alfred O Mueck**	Germany	Zürcher Kreis working group

Joseph Neulen **Petra Stute** **Christian Thaler** **Inka Wiegratz** **Ludwig Wildt**		
Alexander Katalinic **Maria Noftz** **Juan A Garcia-Velasco** **Lee P Shulman** **John N van den Anker** **Jerome F Strauss III**	Germany	International research group REASSURE:
José María Regalado Pedrajas	Spain	Onafiv, Fertilidad y Ginecología, S. L.
Emad Darwish	Egypt	Integrated Fertility Centre, Alexandria, Egypt
Hassan Sallam	Egypt	Alexandria Fertility and ART Centre International Representative Committee of the Royal College of Obstetricians and Gynaecologists in Egypt
Saghar Salehpour	Iran	Iranian Society of Reproductive medicine (ISRM)
Emre Goksan Pabuccu	Turkey	Association of Infertility Medicine and Surgery (UTCD), Turkey
Christophe Blockeel **Christos Venetis** **Biljana Popovic** **Ying Cheong** **Alexandra Freis**	Belgium Greece Serbia UK Norway	ESHRE SIG Reproductive Endocrinology
Yun Sun **Lei Jin** **Juanzi Shi** **Fenghua Liu** **Songying Zhang** **Cuilian Zhang** **Guimin Hao** **Jichun Tan** **Junhao Yan** **Qun Lv** **Jianqiao Liu** **Feiyang Diao** **Xiru Liu** **Yan Zhao** **Rong Li**	China	The Chinese Expert Review Panel for ESHRE OS Guideline
Veaceslav Mosin	Moldova	Alternativa Clinic

Jayesh Amin	India	Nova Wings Fertility Chains
	Germany	German Society of Reproductive Medicine
Alexandra Kohl Schwartz	Switzerland	Ager Switzerland, working group for gynaecological endocrinology and reproductive medicine
Adrija Kumar Datta **Stuart Campbell** **Geetta Nargund**	UK	International society for mild approaches for assisted reproduction (ISMAAR)

Individual experts

Reviewer	Country
Raj Mathur	UK
Natalia Pedachenko	Ukraine
K. K. Pandey	India
Nodira Ruzieva	Uzbekistan
Vyacheslav Lokshin	Kazakhstan
Anagani Manjula	India
Sujoy Dasgupta	India
Mita Aggarwal	India
Namita Kotia	India
Sridevi Nellimarla	India
Padmaja Veeramachaneni	India
Tetiana Tutchenko	Ukraine
Fei Gong	China
Sonia Naik	India
Raoul Orvieto	Israel
Biswajyoti Guha	India
Shikha Gupta	India
Suyesha Khanijao	India
Qinjie Tian	China
Ginny Gupta	India
Surinder Pal Singh Kochar	India
Alberto Revelli	Italy
Tamal Bhattacharyya	India
Mukesh Gupta	India

Sunita Arora	India
Ritu Joshi	India
Dubrovina Svetlana	Russia
Debankur Barman	India
Monu Pattanayak	India
Arnab Bhowmik	India
Bharat S.	India
Puja Kumari	India
Meeta Meeta	India
Ahmed Samy Abdelazim Saad	Egypt
Padmaja veeramachaneni	India
Ahmed Elsayed Hassan Hamed Elbohoty	UAE
Ulughbek Jabborov	Uzbekistan
Tian-Min Ye	China
Yan Gong	China
Jyothi G S	India
Nisha bhatnagar	India
Olena Yashyna	Ukraine
Priti Arora Dhamija	India
Isabel De Almeida	Brazil
Ritesh Sinha	India
Pavika Lal*	India
Manju Khemani	India
Poornima Durga	India
Farrukh Naheed	Pakistan
Feruza Gafurova	Uzbekistan
Geeta Khanna	India
Yun Sun	China
Elena Grudnitskaya	Republic of Belarus
Ayman Hany Ahmed	Egypt
Sandro C. Esteves	Brazil
Hassan Mostafa Gaafar	Egypt
Hisham A. Arab	Saudi Arabia
Yullia*	Ukraine

Diane De Neubourg	Belgium
Aniruddha Bhattacharjee	India
Semra Kahraman	Turkey
Yasser Orief	Egypt
Farah Gari	Algeria
Chengyan Deng	China
Xiu Luo	China
Sabirova Venera	Russia
Aleksandra Khramtsova	Russia
Juan-Enrique Schwarze **Shiv Gupta** **Susana Montenegro***	Germany
Xi Dong	China
Tapilskaya Natalia	Russia
Mohamed Ashraf Mohamed	Egypt
Yasser El Kassar	Egypt
Mitranovici Melinda Ildiko	Romania
Roberto Matorras	Spain
Dongzi Yang	China
Eduardo Correa Allende*	
Shamugiya Nato	Georgia
Umesh N Jindal	India
Madhu Shrivastav	India
Maneesha Jain	India
Anima Prasad	India
Aboubakr Mohamed Elnashar	Egypt
Willem Verpoest	The Netherlands
Guivarc'h Leveque Anne	France
Fang Xiong **Yinyang Bai**	China
Xi Xia	China
Sandeep Karunakaran	India
Sharda Jain	India
Kanad Dev Nayar	India
Kanad Dev Nayar	India

Manpreet Sharma	India
Miaoxin Chen	China
Andrii Berbets	Ukraine
Matthias Mueller*	Switzerland
Shaily Agarwal	India
Rishma Dhillon Pai	India
Rekha Rani	India
Amr Abdel Aziz Nadim	Egypt
Ayman Abo El Nour	Egypt
T. Ramani Devi	India
Pedro Augusto Araujo Monteleone	Brazil
Gavisova Alla	Russia
Monica Varma	India
Gatagazheva Aza Aslanovna	Russia
Tatyana Pestova	Russia
Kasi V Sellappan	India
Robert Fischer	Germany
Srilatha Gorthi	India
Surveen Ghumman	India
Alberto Vaiarelli	Italy
Ayman Oraif	Saudi Arabia
Kokkoni Kiose	Greece
Apostolos Tsironis	UK
Roberto de Azevedo Antunes	Brazil
Michael H. Dahan	Canada
Teraporn Vutyavanich	Thailand
Suresh Nair	Singapore
Nayana Patel	India
Sadiah Ahsan	Pakistan
Philippe Pinton*	Denmark
Alessandro Conforti **Robert Fisher** **Peter Humaidan** **Carlo Alviggi**	Italy Germany Denmark
Kastubh Kulkarni	India

Sonia Malik	India
Colin Howles	Switzerland
Karolina Palinska-Rudzka	UK
Vardanyan Rusudan	Armenia
Mohamed Bedis Chanoufi	Tunisia
BV Shobha	India
Himabindu Annamraju	India
Marianne Vendola	UK
Mekhala Dwarakanath B	India
Liudmila Stavinskaia	Republic of Moldova
Stefan Matik	North Macedonia
Cedrin Durnerin	France
Abdellatif Elkholy	Egypt

CHANGE LOG

Section	Change Description	Version	Publication date
All	Full revision of the guideline	Oct 2025	10-14-2025
6.A r-hFSH biosimilar preparations	The section titled recombinant (r-hFSH) biosimilar preparations has been temporarily removed from the guideline while the guideline group conducts a further review of the evidence and conclusions.	Oct 2025_v2.1	10-29-2025
Change log	A version history of changes to the guideline was added.	Nov 2025_v2.2	11-13-2025