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Ovarian stimulation

POCKET GUIDELINE

Introduction

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

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

In 2019, ESHRE published a guideline on OS for IVF/ICSI, which was updated in 2025, aiming to provide clinicians with evidence-based information on the different options for OS for IVF/ICSI, taking into account issues such as the 'optimal' ovarian response, live birth rates (LBR), safety, patient compliance, and individualisation. In this new guideline, special attention has also been given to pre- and adjuvant treatments in LOW responders and the prevention of ovarian hyperstimulation syndrome (OHSS) in HIGH responders.

Guideline scope

This pocket guideline aims 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, LBR, safety, patient compliance, and individualisation. Knowledge gaps were identified and prioritised. This pocket guideline provides a summary of the 121 recommendations from the ESHRE Ovarian Stimulation for IVF/ICSI guideline update of 2025: 42 recommendations remained unchanged from 2019, 4 recommendations were reworded for better understanding, 29 recommendations were updated in view of new evidence, and 46 new recommendations for 2025 have been formulated.

We have added the following symbols to explain the strength of the recommendations:

Recommendation based on research evidence

Recommendation based on considered opinion of the guideline development group

The full guideline is available on the website of ESHRE: www.eshre.eu/guidelines.

Colour codes

Dark blue: recommended

Light blue: can be considered in specific circumstances

Red: not recommended

Terminology

Response after ovarian stimulation is usually classified as poor, normal and excessive. However, this terminology can be potentially stigmatising/traumatising towards patients. Therefore, the guideline development group (GDG) would like to propose to use the terminology low, normal and high response to categorise (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), characterised 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 characterise 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, characterised 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 characterise a low response.

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.

Pre-treatment phase

Interventions that are recommended

Pre-stimulation evaluation

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

Pre-treatment therapies

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

Pre-treatment therapies

Pre-treatment with hCG can only be used in the context of a clinical trial.

Interventions that should not be routinely performed

Pre-treatment stimulation evaluation

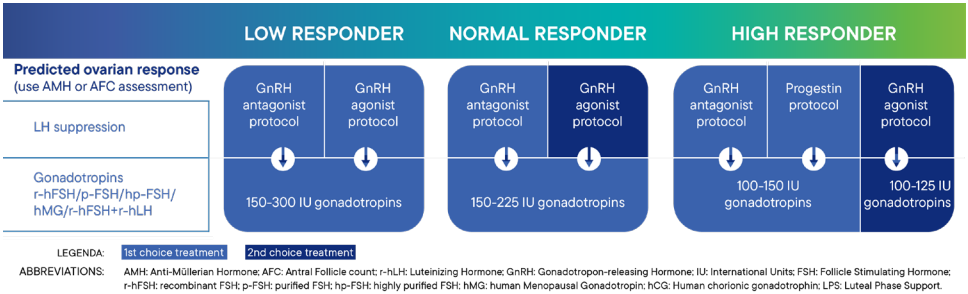
- Age, BMI, basal FSH, inhibin B, basal oestradiol, basal progesterone and basal LH for the prediction of ovarian response.
- AFC, AMH, basal FSH, basal LH, basal oestradiol, basal progesterone and inhibin B for the prediction of pregnancy and live birth.

Pre-treatment therapies

- Pre-treatment with oestrogen before ovarian stimulation using the GnRH antagonist protocol.
- Pre-treatment with progesterone before ovarian stimulation.
- Pre-treatment with combined oral contraceptive pill (COCP) in the GnRH antagonist protocol with FSH alone stimulation.
- Pre-treatment with GnRH antagonist before ovarian stimulation in a delayed-start gonadotrophin protocol is probably not recommended.

Pituitary suppression and ovarian stimulation

Interventions that are recommended



Response-based stratification

- A reduced gonadotropin dose (100 to <150 IU) is probably recommended to decrease the risk of OHSS in predicted high responders.
- The GnRH antagonist protocol is recommended for predicted high responders.
- 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.

Pituitary suppression

- The GnRH antagonist protocol is recommended over the GnRH agonist protocols given the comparable efficacy and higher safety in the general IVF/ICSI population.
- The fixed GnRH antagonist protocol is probably recommended over the flexible GnRH antagonist protocol.
- If freeze-all is planned, the use of progestin for pituitary suppression is probably equally recommended to GnRH analogues.

Type of stimulation drug

The use of the following stimulation drugs is equally recommended:

- Recombinant human FSH (r-hFSH) vs Human menopausal gonadotropin (hMG)
- r-hFSH vs Purified FSH (p-FSH)
- r-hFSH vs Highly purified FSH (hp-FSH)
- r-hFSH vs the combination of r-hFSH + r-hLH
- Long-acting r-hFSH vs daily
- Follitropin delta vs follitropin alpha/beta
- hp-FSH vs hMG

Adjustment of gonadotropin dosage

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.

Non-conventional start of ovarian stimulation

- 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.

- Luteal start ovarian stimulation could be used when a fresh transfer is not intended and there is no possibility of natural conception.

- Double stimulation can be used with the intention to accumulate oocytes or embryos when fresh transfer is not planned.

Pituitary suppression

If GnRH agonists are used, the long GnRH agonist protocol is recommended over the short or ultrashort GnRH agonist protocol.

Interventions that should not be routinely performed

Response-based stratification

- Delayed-start ovarian stimulation for predicted high responders to decrease the risk of OHSS.

- Delayed-start ovarian stimulation over a conventional gonadotrophin dose for predicted normal responders.

- Neither a reduced nor increased gonadotrophin dose over a conventional gonadotrophin dose (equivalent to 150–225 IU) for predicted normal responders.
- Delayed start ovarian stimulation for predicted low responders.
- Modified natural cycle over conventional stimulation for low responders.
- A gonadotropin dose higher than 300 IU for predicted low responders.

Type of stimulation drug

- The combined use of recombinant human FSH (rFSH) with human menopausal gonadotropin (hMG), either from the start or mid-phase of ovarian stimulation, over the use of either r-hFSH or hMG alone in normal and low responders.
- The use of recombinant human LH + recombinant human FSH (r-hFSH+r-hLH) over human menopausal gonadotropin (hMG) in GnRH agonist protocols with regards to safety.
- Adding low dosages of hCG to FSH stimulation.
- The addition of letrozole to gonadotropins in stimulation protocols
- The addition of clomiphene citrate to gonadotropins in stimulation protocols.

Adjustment of gonadotropin dosage

Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during ovarian stimulation.

Adjuncts during ovarian stimulation

The use of the following adjuncts during ovarian stimulation:

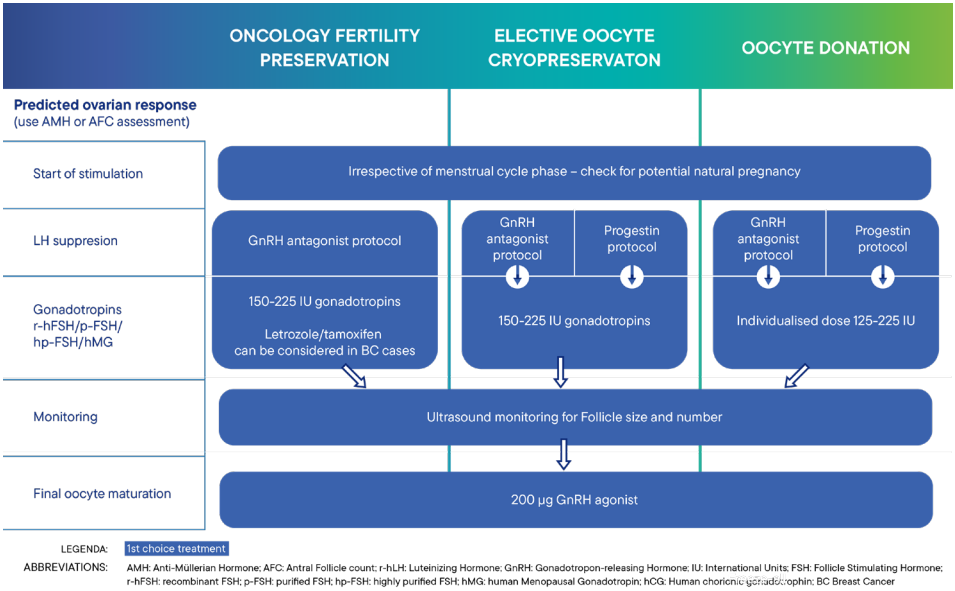
- Metformin for women with PCOS
- Growth hormone
- Testosterone for low responders
- DHEA for low or normal responders
- Aspirin
- Sildenafil for low responders
- Myo-inositol

Non-conventional start of ovarian stimulation

Late luteal phase start of gonadotropins with fresh transfer for low responders.

Fertility preservation and oocyte donation

Interventions that are recommended



Fertility preservation in patients facing gonadotoxic treatment

- Double stimulation can be considered for urgent fertility preservation cycles.
- For patients facing gonadotoxic treatment, ovarian stimulation for fertility preservation should be started irrespective of the menstrual cycle phase.
- For ovarian stimulation in women seeking fertility preservation for medical reasons the GnRH antagonist protocol is recommended.
- 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.
- For final oocyte maturation in patients facing gonadotoxic treatment, GnRH agonist is preferred.

Elective oocyte cryopreservation

- Ovarian stimulation for elective oocyte preservation can be started irrespective of the menstrual cycle phase.
- GnRH antagonist or progestin protocol are probably recommended over GnRH agonist protocols for pituitary suppression in elective oocyte cryopreservation.
- For final oocyte maturation in elective oocyte cryopreservation, GnRH agonist is preferred.

Oocyte donation

- Conventional follicular start or random-start ovarian stimulation are equally recommended for oocyte donation cycles.
- If random-start ovarian stimulation is used, oocyte donors need to adopt contraceptive measures to prevent the possibility of a natural pregnancy.
- Any type of contraception (hormonal, non-hormonal, oral, vaginal or intrauterine) can be used before initiation of ovarian stimulation in oocyte donors.
- Progestin or intrauterine contraception can be used during ovarian stimulation in oocyte donors.
- For pituitary suppression in oocyte donors the GnRH antagonist and progestin protocol are probably equally recommended.
- 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.
- Gonadotropin dose should be individualised based on ovarian reserve with the goal to maintain donors' safety and also to obtain an optimal number of oocytes.
- The routine use of a GnRH agonist trigger is recommended in oocyte donors using the GnRH antagonist or progestin protocols for pituitary suppression.

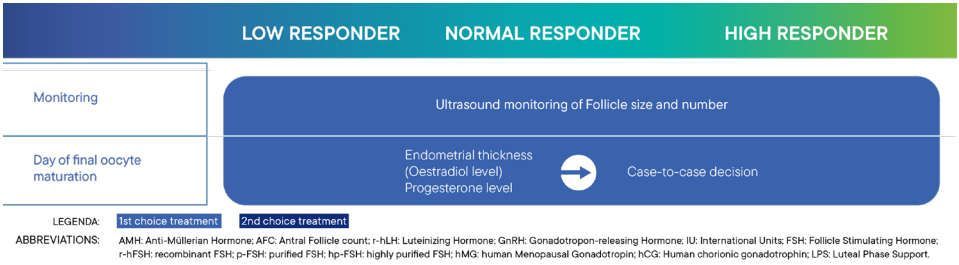
Interventions that should not be routinely performed

Oocyte Donation

- A GnRH agonist protocol for pituitary suppression.
- The use of a hCG trigger.

Monitoring

Interventions that are recommended



Endometrial Thickness

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

Criteria for final oocyte maturation

- 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.
- 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.

Hormonal assessments on day of final oocyte maturation

- It is probably recommended to measure serum progesterone levels on the day of final oocyte maturation in cycles aimed for a fresh embryo transfer.
- 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).

Cycle cancellation

- The physician should counsel the individual unexpected low responder regarding pregnancy prospects and decide individually whether to continue this cycle.
- 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.
- In GnRH antagonist cycles, withholding GnRH agonist triggering may still be considered in women with extremely high ovarian response.

Interventions that should not be routinely performed

Hormone assessments

- The addition of oestradiol measurements to ultrasound monitoring.
- The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring.

Endometrial thickness

Routine monitoring of endometrial thickness during controlled ovarian stimulation.

Criteria for final oocyte maturation

- Timing of final oocyte maturation triggering based on oestradiol levels alone.
- Timing of final oocyte maturation based on oestradiol/follicle ratio alone.

Hormonal assessments on day of final oocyte maturation

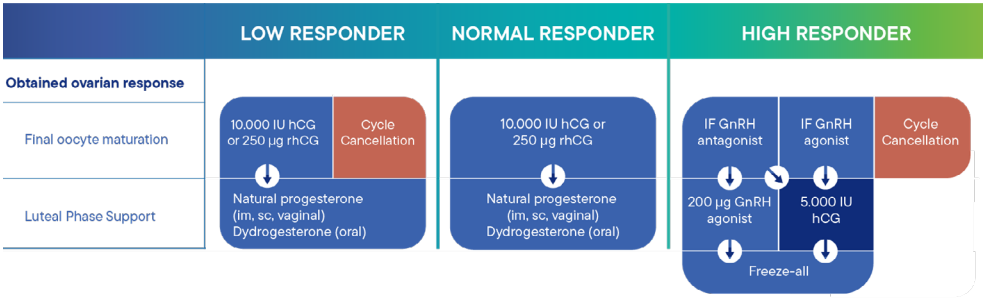
- Measurement of serum oestradiol levels on the day of hCG trigger in ovarian stimulation cycles with an intent for a fresh embryo transfer.
- Measurement of serum LH levels on the day of hCG trigger in ovarian stimulation cycles aimed for a fresh embryo transfer.
- Measurement of serum oestradiol, progesterone or luteinizing hormone levels on the day of a GnRH agonist trigger in freeze-all cycles.

Cycle cancellation

A low response to ovarian stimulation alone is not a reason to cancel a cycle.

Triggering ovulation and luteal support

Interventions that are recommended



LEGENDA: 1st choice treatment 2nd choice treatment

ABBREVIATIONS: AMH: Anti-Müllerian Hormone; AFC: Antral Follicle count; r-hLH: Luteinizing Hormone; GnRH: Gonadotropon-releasing Hormone; IU: International Units; FSH: Follicle Stimulating Hormone; r-hFSH: recombinant FSH; p-FSH: purified FSH; hp-FSH: highly purified FSH; hMG: human Menopausal Gonadotropin; hCG: Human chorionic gonadotrophin; LPS: Luteal Phase Support.

Type of drug for final oocyte maturation

- The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation in ovarian stimulation protocols.
- 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.

Luteal support

- Progesterone is recommended for luteal phase support after IVF/ICSI.
- Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used.
- 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 micronised vaginal progesterone in-oil capsules;
- 100 mg two or three times daily for micronised vaginal progesterone in starch suppositories;
- 400 mg two times daily for vaginal pessary.

- 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.
- Progesterone support should be administered until at least the day of the pregnancy test.
- Dydrogesterone is probably recommended for luteal phase support.



Luteal Support

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

Interventions that should not be routinely performed

Type of drug for final oocyte maturation

The following drugs for final oocyte maturation:

- Recombinant LH.
- GnRH agonist for the general IVF/ICSI population with fresh transfer, regardless of luteal phase support (with or without LH-activity).
- The addition of a GnRH agonist to hCG as a dual trigger for normal or low responders.

Luteal support

The following drugs for luteal support:

- The addition of oestradiol to progesterone
- hCG 1500 IU in hCG-triggered cycles
- A GnRH agonist bolus, alone or in addition to progesterone
- Repeated GnRH agonist injections, alone or in addition to progesterone

Prevention of OHSS

Interventions that are recommended

- 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.
- If the GnRH agonist trigger with triptorelin is applied, dosages ranging between 0.1–0.4 mg can be chosen.
- 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.
- 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.
- 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.
- Dopamine agonists are recommended to decrease the risk of early OHSS, particularly in patients receiving hCG for final oocyte maturation.
- A freeze-all strategy is recommended to minimise the risk of late-onset OHSS.
- 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.

Interventions that should not be routinely performed

The addition of hCG to GnRH agonist as a dual trigger for final oocyte maturation for high responders.

References

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The updated guideline on Ovarian Stimulation, was developed by a multidisciplinary guideline development group.

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