National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

Supporting document for the recommendations on ovarian stimulation in IVF

NICE guideline NG257

Evidence underpinning recommendations 1.40, 1.43 to 1.46 and 1.53.6 in the NICE guideline

March 2026

Final

This supporting document was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN: 978-1-4731-9405-2

Contents

Ovarian stimulation in IVF

Objective

The objective of this update is to revise recommendations on ovarian stimulation in IVF.

Introduction

Ovarian stimulation with gonadotropins is used as part of IVF to increase the number of oocytes available for fertilisation. The aim is to increase the number of embryos from which a choice can be made for transfer. The procedure aims to induce the development of multiple mature oocytes that can be surgically retrieved prior to fertilisation in the laboratory.

Methods and process

According to the scope of the update to the NICE Fertility problems guideline consulted on and published in 2022, it was agreed that no evidence reviews would be carried out in relation to ovarian stimulation in IVF. Instead, it was decided to stand down the relevant recommendations and consider cross-reference to guidance from other developers, such as the European Society of Human Reproduction and Embryology (ESHRE) guideline on Ovarian stimulation in IVF/ICSI (from 2019 at the time, updated in 2025)[1].

Recommendations from guidelines by other developers are only cross-referred to in a NICE guideline if both the guideline development process and recommendations have been appraised and assessed as appropriate for use within NICE guidelines. The ESHRE guideline on Ovarian stimulation in IVF/ICSI was critically appraised by 2 reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. The AGREE II instrument is an internationally validated tool that is used to assess the methodological rigour and transparency of clinical practice guidelines. For summary of the criteria for assessing guidelines using the AGREE II tool see Appendix A, summary of the external guideline and AGREE II tool assessment, see Appendix B, reviewer scoring of the ESHRE guideline using AGREE II tool, see Appendix C.

A small expert working group consisting of guideline committee members (2 consultant gynaecologists, 1 lay member and the committee chair) reviewed each applicable ESHRE guideline section and together with the NICE technical team processed these changes according to NICE's methods and processes for cross-referring to guidance from other developers. See Appendix D for discussion points for assessing ovarian stimulation in IVF recommendations. The rest of the guideline committee members were informed about these changes with an opportunity to respond.

At the time of updating in March 2026, the latest update to the ESHRE guideline on Ovarian stimulation in IVF/ICSI was version 2.2. The NICE expert working group were aware the ESHRE guideline is due to be further updated to include a section on recombinant (r-hFSH) biosimilar preparations (version 2.3), however recommendations on this were not assessed during this update and therefore are not intended to be included in references to the ESHRE guideline.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Included evidence

The following sections of the ESHRE guideline on Ovarian stimulation in IVF/ICSI were included:

- Part B: Pre-treatment therapies (NG257 recommendation 1.40)

- Part C: Pituitary suppression and ovarian stimulation (NG257 recommendation 1.43)
- Part D: Fertility preservation and oocyte donation (NG257 recommendation 1.53.6)
- Part E: Monitoring (NG257 recommendation 1.44)
- Part F: Triggering ovulation & luteal support (NG257 recommendation 1.45)
- Part G: Prevention of ovulation hyperstimulation syndrome (OHSS) (NG257 recommendation 1.46)

Part A of the ESHRE guideline covers pre-stimulation evaluation, including ovarian response prediction and pregnancy prediction. NICE evidence review A already covers ovarian reserve testing, therefore, this part of the ESHRE guideline was not included.

The committee's discussion and rationale for recommendations

This section discusses the relevant recommendations on ovarian stimulation in IVF/ICSI from the ESHRE guideline (2025) that are cross-referenced in the NICE guideline on fertility problems: assessment and treatment (NG257).

Rationale

The ESHRE guideline was developed following its established guideline development process, with recommendations based on the available evidence and consensus from its Guideline Development Group (GDG). An assessment using the AGREE II instrument rated the guideline to be sufficient for use, leading NICE to cross-reference the relevant sections of the guideline. The guideline was assessed as well conducted, with recommendations that were well thought through and clearly linked to the supporting evidence, despite some methodological limitations.

The expert working group reviewed each section of the ESHRE guideline and agreed that each of the recommendations cross-referenced in NG257 were relevant, useful and would not result in significant resource implications or significant changes to current clinical practice.

The expert working group discussed the fact that many of the ESHRE recommendations on ovarian stimulation are based on the premise that patients should be categorised into high, normal or low responders. They agreed that the principle that dosage of gonadotropin treatment should depend on the individual's predicted response was consistent with the NICE guideline recommendations.

They also noted the ESHRE recommendations on pituitary suppression regimens include the use of progestin, with one option being freely available in the UK and the other available as hormone replacement therapy (HRT) only. However, it can be prescribed off-label and therefore the recommendations are still applicable within a UK context.

The expert working group discussed whether there were any health inequalities issues which could arise as a result of the ESHRE recommendations. They noted the recommendations do not use gender-additive language and therefore do not specifically cover trans or non-binary people but agreed that generally the ESHRE recommendations are applicable to trans men and non-binary people with female reproductive organs. There are additional considerations and aspects of care for this population that are not covered by the ESHRE recommendations such as extra information and support needs, and the potential need to discuss a pause in gender-affirming hormones during ovarian stimulation. The committee acknowledged that these aspects are not covered by the NG257 either but concluded that health professionals are expected to use their clinical judgement, and thus no additional recommendations were made. The committee also discussed that the ESHRE recommendations are primarily intended for health professionals rather than patients and may therefore be difficult for patients to understand. However, a patient version of the ESHRE guideline is available on the guideline's website, which is written in plain language

and designed to improve accessibility and implementation.

Cost effectiveness and resource use

No health economic evaluation or formal cost-effectiveness analysis was conducted for the ESHRE guideline, and resource impact was assessed only 'where relevant'. As these discussions are not detailed in the guideline, it is unclear whether resource implications were considered during the development of the recommendations. Although the ESHRE guideline development manual outlines processes for evaluating guideline impact through clinical audits and indicators, no auditing or monitoring criteria are provided for this guideline. However, the guideline committee made a qualitative assessment based on their expertise and experience that implementing the relevant ESHRE recommendations would be cost-effective for the NHS and would not result in significant resource implications, as they largely align with current practice and many of them recommend against the use of certain interventions. The committee discussed the fact that some of the recommendations could even result in cost and resource saving, for example recommendations against higher dosing, potentially leading to a lower cost per cycle.

Recommendations supported by this document

This supporting document underpins recommendations 1.40, 1.43 to 1.46 and 1.53.6.

References

1. Ovarian stimulation for IVF/ICSI. Guideline of European Society of Human Reproduction and Embryology. The ESHRE Ovarian Stimulation guideline Group; 2025. Available from: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI

Appendices

Appendix A Criteria for assessing guidelines using AGREE II tool

The external guideline was appraised using a two-stage process. The first stage assessed whether the external guideline development process was robust and high quality. This was conducted using the AGREE II instrument.

The second stage of the appraisal process assessed the applicability and acceptability of the external recommendations themselves. It covered areas that are important for NICE such as the quality of the guideline development process, barriers to implementation, compatibility with cultures and values and health inequalities.

First stage assessment using the AGREE II instrument:

The AGREE instrument was developed to address the issue of variability in guideline quality. To that end, the AGREE instrument is a tool that assesses the methodological rigour and transparency in which a guideline is developed. The original AGREE instrument has been refined, which has resulted in the new AGREE II.

AGREE II has 6 domains and an overall assessment. The domains are listed below:

- Domain 1. **Scope and Purpose** is concerned with the overall aim of the guideline, the specific health questions, and the target population.
- Domain 2. **Stakeholder Involvement** focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users.
- Domain 3. **Rigour of Development** relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations, and to update them.
- Domain 4. **Clarity of Presentation** deals with the language, structure, and format of the guideline.
- Domain 5. **Applicability** pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline.
- Domain 6. **Editorial Independence** is concerned with the formulation of recommendations not being unduly biased with competing interests.
- Overall assessment includes the rating of the overall quality of the guideline and whether the guideline would be recommended for use in practice.

For further details on each domain see the agree reporting checklist at agreetrust.org

Each of the 23 AGREE II items were rated on a 7-point scale (1 indicating strong disagreement and 7 indicating strong agreement). An overall rating for each of the 6 AGREE II domains was then calculated by summing all the scores of the individual items in a domain and then calculating the total as a percentage of the maximum possible score for that domain, as follows:

$$\frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}} \times 100$$

An overall rating for all domains was then determined (score 1 to 7) and finally an overall percentage rating was calculated for each guidance document based on the following equation: (overall score – 1)/6.

The AGREE II also suggests an overall assessment which includes a rating of the overall quality of the guideline and whether the guideline would be recommended for use in practice. The overall assessment requires the user to make a judgment as to the quality of the guideline, taking into account the criteria considered in the assessment process.

Table 1: Interpretation of overall score

Assessment	**Score**
Not met	equivalent to an AGREE II score of approximately 3 or less
Partially met	equivalent to an AGREE II score of approximately 4-5
No major concerns / fully met	equivalent to an AGREE II score of approximately 6-7

Second stage appraisal of the guideline using NICE checklist:

For the external guideline assessed to be high quality using the AGREE II instrument, the suitability of specific recommendations for cross-referencing in a NICE guideline was assessed using a NICE checklist. The checklist includes discussion points that were developed to provide a structured framework for assessing issues not covered by AGREE II. The discussion points were used to assess the recommendations in more detail in terms of applicability and acceptability. For example, they include questions on health inequality considerations, applicability to UK settings, compatibility with cultures and values and consideration of health economics. Please see Appendix C for discussion points for assessing recommendations on ovarian stimulation in IVF recommendations.

Appendix B Summary of external guideline and its AGREE II assessment

Study	Population	Recommendations	Quality assessment with AGREE II
The ESHRE Guideline Group on Ovarian Stimulation 2025[1] ESHRE Guideline on Ovarian Stimulation for IVF/ICSI (Update 2025) Study type: Guideline Aim: 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.	Infertility specialists and specialty nurses performing the daily care for patients undergoing ovarian stimulation for the purpose of IVF/ICSI.	This guideline summarises current evidence and offers a consensus view on different options for the performance of ovarian stimulation for IVF/ICSI. **Recommendations:** **Part A: Pre-stimulation evaluation** This section of the ESHRE guideline was not included because it is covered by Evidence review A of the NICE guideline NG257. **Part B: Pre-treatment therapies** Pre-treatment therapies • Pre-treatment with oestrogen before ovarian stimulation using the GnRH antagonist protocol is not recommended for improving efficacy. [updated] • Pre-treatment with progesterone before ovarian stimulation is probably not recommended for improving efficacy. [reworded] • Oestrogen or progesterone pre-treatment can be used for scheduling purposes given the data on efficacy and safety. [reworded] • COCP pre-treatment is not recommended in the GnRH antagonist protocol with FSH alone stimulation, because of reduced efficacy. [updated] • 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] • GnRH antagonist pre-treatment before ovarian stimulation in a delayed-start gonadotrophin	**Scope and Purpose** **78%** The guideline's scope and purpose is clearly explained at the start of the document and throughout, as well as topics or issues outside its scope. Evidence review questions are clearly stated and easy to find, but specific details about PICOs can only be broadly determined from descriptions of the evidence and are not specifically defined. The population of interest is broadly defined, as are excluded populations. Additional detail could be provided about the included population, but the description might be deliberately inclusive. **Stakeholder Involvement** **78%** Members of the guideline development group (GDG), including the person who provided methodological support, are clearly identified alongside information which shows they have appropriate expertise for the topic, although specific information about each member's discipline is not given. The target users of the guideline are clearly defined, as well as how the guideline can be used. This target populations (infertility specialists and specialty nurses) are represented in the GDG, and their views and preferences have been sought through a consultation process. However, the population who the guideline applies to (people undergoing ovarian stimulation for the purpose of IVF/ICSI) have not been represented within the GDG

		protocol is probably not recommended. [2019] • hCG pre-treatment can only be used in the context of a clinical trial. [2025] **Part C: Pituitary suppression and ovarian stimulation** Ovarian stimulation protocols • Delayed-start ovarian stimulation is probably not recommended routinely in predicted high responders to decrease the risk of OHSS. [2025] There is no evidence to justify the use of NC or MNC for OS in high responders. • A reduced gonadotropin dose (100 to < 150 IU) is probably recommended to decrease the risk of OHSS in predicted high responders. [2025] • The GnRH antagonist protocol is recommended for predicted high responders. [updated] • Delayed-start ovarian stimulation is probably not recommended over a conventional gonadotrophin dose for predicted normal responders. [2025] • 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] • Delayed start ovarian stimulation is probably not recommended for predicted low responders. [2025] • The use of modified natural cycle is probably not routinely recommended over conventional stimulation for low responders. [updated] • 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] • A gonadotropin dose higher than 300 IU is not recommended for predicted low responders.	composition, and no patient representatives or relevant groups appear to have been included in consultation. A patient version of the guideline is available, but patient views do not appear to have been sought during development of the guideline. **Rigour of Development** **69%** The databases and time period for the searches are provided but the full search strategy, including search terms, are not provided. Although excluded studies and the reasons for their exclusion are listed in an appendix, protocols for each review question, inclusion and exclusion criteria, and PICOs are not provided. Narrative descriptions of the strengths and limitations of the body of evidence are provided, including methodological limitations and an assessment of the consistency of the evidence, but this is limited to the critical outcomes. GRADE summary of evidence tables are provided in an appendix which provide further information about certainty of the evidence, again only for critical outcomes. Details about how recommendations are formulated are provided in a separate guideline development manual which is signposted to in the guideline, but specific information about the GDG's discussions, decision-making, and how they reached consensus is not provided. Detailed information is given about interpretation of the evidence and how this informed recommendations, including consideration of the benefits of interventions, but this is not consistently balanced against risks based on either the evidence or the GDG's knowledge and expertise. There is an explicit link between the evidence found and the recommendations made,

		[2019] Pituitary suppression regimens • If GnRH agonists are used, the long GnRH agonist protocol is recommended over the short or ultrashort GnRH agonist protocol. [updated] • 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] • The fixed GnRH antagonist protocol is probably recommended over the flexible GnRH antagonist protocol. [2025] • If freeze-all is planned, the use of progestin for pituitary suppression is probably equally recommended to GnRH analogues. [updated] Types of gonadotropins & stimulation drugs • The use of recombinant human FSH (r-hFSH) and human menopausal gonadotropin (hMG) for ovarian stimulation is equally recommended. [2019] • The use of recombinant human FSH (r-hFSH) and purified FSH (pFSH) for ovarian stimulation in GnRH agonist protocol is equally recommended. [2019] • 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] • The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for the general IVF population. [2025] • The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended for low responders. [2025] • The combination of r-hFSH with r-hLH and r-hFSH alone are probably equally recommended	including strength of the recommendations and when there was a lack of evidence. A guideline consultation period was held, with information available in the guideline development methods document. Organisations and individuals consulted, stakeholder comments and the GDG's responses are available in a separate report, but this document is not signposted to or easily findable on the ESHRE website. A procedure and timeline for updating the guideline is clearly provided. **Clarity of Presentation** **81%** The majority of recommendations are clear and specific, but where the strength of the evidence has affected the ability to make strong recommendations, vague wording is occasionally used which can make it difficult to interpret the guidance. Different options for the management of ovarian stimulation are usually presented. All recommendations are presented in a list at the beginning of the document as well as throughout, making them easily findable. No key recommendations are identified. **Applicability** **46%** It is stated that GDG members were asked to identify recommendations that would be difficult to implement but it is unclear whether this happened as neither these recommendations nor their barriers are described in the guideline. An implementation strategy is provided, including some facilitators for the guideline more broadly, but not for specific recommendations. This strategy provides information about publication and dissemination plans to improve implementation, and some tools are available on

		for women of advanced age (≥35 year). [2025] • 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] • The use of long-acting and daily recombinant human FSH (r-hFSH) is equally recommended in GnRH antagonist cycles for normal responders. [2019] • Follitropin delta and follitropin alpha/beta are equally recommended for ovarian stimulation. [2025] • The use of highly purified FSH (hp-FSH) and human menopausal gonadotropin (hMG) for ovarian stimulation in GnRH agonist protocols is equally recommended. [2019] • The use of recombinant human LH + recombinant human FSH (rhFSH+r-hLH) for ovarian stimulation is probably not recommended over human menopausal gonadotropin (hMG) in GnRH agonist protocols with regards to safety. [2019] • Adding low dosages of hCG to the FSH stimulation is probably not recommended. [2025] • The addition of letrozole to gonadotropins in stimulation protocols for predicted high responders is probably not recommended. [updated] • The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders. [2019] • The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted low responders. [2019]	the ESHRE guideline to aid understanding and accessibility, including a patient version of the guideline. No health economic evaluation or formal analysis of cost-effectiveness was performed for the guideline, and resource impact was only assessed 'where relevant'. These discussions are not detailed in the guideline so it is unclear if resource impact was considered during development of the recommendations. The ESHRE guideline development manual details their processes for evaluating guideline impact using a clinical audit and indicators, but no monitoring or auditing criteria are provided for this guideline. **Editorial Independence** **100%** The guideline was developed and funded by ESHRE, and a statement of editorial independence is made. GDG members are independent topic experts who did not receive payment for their participation beyond the reimbursement of travel expenses, and information is provided about how ESHRE maintains objectivity and independence in its guideline development manual. Conflicts of interest of the GDG members are recorded and described in detail in a guideline appendix, and information about how conflicts of interest are handled is described in the guideline development manual.

		• There is no evidence available to recommend the substitution of FSH by Clomiphene Citrate in ovarian stimulation. • The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted high responders. [2019] • The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders. [2025] • Clomiphene citrate alone or in combination with gonadotrophins, and gonadotropin stimulation alone are probably equally recommended for predicted low responders. [updated] Adjustment of gonadotropin dose • Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during ovarian stimulation is probably not recommended. [2019] • 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] Adjunct therapies • 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] • Use of adjunct growth hormone before and/or during ovarian stimulation is not recommended for normal responders. [2025] • Use of adjunct growth hormone before and/or during ovarian stimulation is probably not recommended for low responders. [Updated]	

		• Use of adjunct growth hormone before and/or during ovarian stimulation is not recommended for women with PCOS. [2025] • Use of testosterone before ovarian stimulation is probably not recommended for low responders. [updated] • Use of DHEA before and/or during ovarian stimulation is not recommended for low responders. [2019] • Use of DHEA before and/or during ovarian stimulation is not recommended for normal responders. [2025] • Use of aspirin before and/or during ovarian stimulation is not recommended in the general IVF/ICSI population nor for low responders. [2019] • Use of sildenafil before and/or during ovarian stimulation is not recommended for low responders. [2019] • Use of myo-inositol before and/or during ovarian stimulation is probably not recommended for women with PCOS undergoing IVF. [2025] • Use of myo-inositol before and/or during ovarian stimulation is not recommended in low responders. [2025] • Use of myo-inositol before and/or during ovarian stimulation is not recommended in non-PCOS women undergoing IVF. [2025] Non conventional start • 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] • Luteal start ovarian stimulation could be used when a fresh transfer is not intended and there is	

		no possibility of natural conception. [Updated] • Late luteal phase start of gonadotropins with fresh transfer is probably not recommended for low responders. [Updated] • Double stimulation can be considered for urgent fertility preservation cycles. [2019] • Double stimulation can be used with the intention to accumulate oocytes or embryos when fresh transfer is not planned. [Updated] **PART D – Fertility preservation & oocyte donation** Fertility preservation for patients facing gonadotoxic treatment • For patients facing gonadotoxic treatment, ovarian stimulation for fertility preservation should be started irrespective of the menstrual cycle phase. [updated] • For ovarian stimulation in women seeking fertility preservation for medical reasons the GnRH antagonist protocol is recommended. [2019] • 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] • For final oocyte maturation in patients facing gonadotoxic treatment, GnRH agonist is preferred. [2025] Elective oocyte cryopreservation • Ovarian stimulation for elective oocyte preservation can be started irrespective of the menstrual cycle phase. [2025] • GnRH antagonist or progestin protocol are probably recommended over GnRH agonist protocols for pituitary suppression in elective oocyte cryopreservation. [2025] • For final oocyte maturation in elective oocyte	

		cryopreservation, GnRH agonist is preferred. [2025] Oocyte donation This section of the ESHRE guideline is not in scope for the NICE guideline update. **PART E – Monitoring** Hormonal assessment during stimulation • The addition of oestradiol measurements to ultrasound monitoring is probably not recommended. [2019] • The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring is probably not recommended. [2019] Endometrial thickness • Routine monitoring of endometrial thickness during controlled ovarian stimulation is probably not recommended. [2019] • 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] 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. [2019] • 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] • The GDG does not recommend to base timing of final oocyte maturation triggering on oestradiol levels alone. [2019] • The GDG does not recommend to base timing of final oocyte maturation on oestradiol/follicle ratio alone. [2019] Hormonal tests on trigger day • 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] • 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] • 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] • 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] • 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] Criteria for cycle cancellation • A low response to ovarian stimulation alone is	

		not a reason to cancel a cycle. [2019] • The physician should counsel the individual unexpected low responder regarding pregnancy prospects and decide individually whether to continue this cycle. [Updated] • 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] • In GnRH antagonist cycles, withholding GnRH agonist triggering may still be considered in women with extremely high ovarian response. [2025] **PART F – Triggering ovulation & luteal support** Triggering • The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation in ovarian stimulation protocols. [2019] • 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] • It is not recommended to administer recombinant human LH for triggering final oocyte maturation. [2019] • 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] • If the GnRH agonist trigger with triptorelin is applied, dosages ranging between 0.1-0.4 mg can be chosen. [2019] • 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] • The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for low responders. [2025] • There is too limited evidence to draw conclusions on the use of double trigger for final oocyte maturation for IVF/ICSI. Luteal phase support • Progesterone is recommended for luteal phase support after IVF/ICSI. [2019] • Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used. [2019] • 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] • 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] • Progesterone support should be administered until at least the day of the pregnancy test. [2019] • 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. • The addition of oestradiol to progesterone for luteal phase support is probably not recommended. [2019] • In hCG triggered ovarian stimulation cycles, hCG as luteal phase support in standard dosages of 1500 IU is not recommended. [updated] • A GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. [updated] • Repeated GnRH agonist injections, alone or in addition to progesterone for luteal phase support in hCG triggered cycles is probably not recommended. [reworded] • Addition of LH to progesterone for luteal phase support can only be used in the context of a clinical trial. [2019] **PART G – Prevention of OHSS** OHSS prevention • 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] • 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] • The addition of hCG to GnRH agonist as a dual trigger for final oocyte maturation is probably not recommended for high responders. [2025] • 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] • 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] • Dopamine agonists are recommended to decrease the risk of early OHSS, particularly in patients receiving hCG for final oocyte maturation. [2025] • A freeze-all strategy is recommended to minimise the risk of late onset OHSS. [updated] • 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]	
Overall score			**Overall quality of the guideline: 5** (1 lowest possible quality and 7 highest possible quality) **Guideline recommended for use: Yes**

Appendix C AGREE II tool reviewer scoring

	1. Scope and purpose				2. Stakeholder involvement				3. Rigour of development									4. Clarity of presentation				5. Applicability					6. Editorial independence			Overall assessment
Reviewer & guideline	Objectives	Question	Population	Total	Group membership	Target population	Target users	Total	Search methods	Evidence selection criteria	Evidence strengths and limitations	Formulation of recs	Considerations of benefits / harms	Link between recommendations & evidence	External review	Updating procedure	Total	Specific & unambiguous recs	Management options	Identifyable key recs	Total	Facilitators & barriers to application	Implementation advice/tools	Resource implications	Monitoring/auditing criteria	Total	Funding body	Competing interests	Total	
Reviewer 1	7	5	5	**17**	6	4	7	**17**	2	2	4	4	7	6	7	7	**39**	6	7	6	**19**	6	6	3	2	**17**	7	7	**14**	**5**
Reviewer 2	6	5	6	**17**	6	4	7	**17**	3	3	6	5	6	7	6	7	**43**	4	5	7	**16**	4	5	2	2	**13**	7	7	**14**	**5**
Score				**78%**				**78%**									**69%**				**81%**					**46%**			**100%**	

Appendix D Discussion points for assessing ovarian stimulation in IVF recommendations

	Details
Were the recommendations developed in accordance with the external organisation's development process (i.e., the process that has been assessed by AGREE II)?	The ESHRE guideline (update 2025) was developed following its prescribed development process, with recommendations based on current evidence and consensus from the Guideline Development Group (GDG). The guideline was assessed by 2 reviewers from the NICE technical team using the AGREE II instrument. This evaluation included a rating of the overall quality of the guideline and an assessment of whether it should be recommended for use in practice. The guideline was deemed suitable and recommended for use (overall AGREE II tool score 71%). Additionally, the expert working group agreed that the ESHRE guideline is widely adopted and applicable to UK settings. Therefore, NICE decided to cross-reference to the relevant sections of the ESHRE guideline.
Is the recommendation and the guideline development process low risk to NICE (this may be informed by other processes for example risk categories for QA or the multi criteria decision framework for updates)?	According to the expert working group, the recommendations are low risk to NICE and in line with current clinical practice and recent international guideline recommendations. The expert working group agreed that the recommendations referred to were more comprehensive and up to date than the existing NICE recommendations on ovarian stimulation, and therefore it was appropriate that the NICE recommendations were replaced with references to the ESHRE guidance. The expert working group also considered whether the ESHRE recommendations align with NICE recommendations throughout the guideline and noted there is one recommendation in Part A: Pre-stimulation evaluation whereby ESHRE recommend against using antral follicle count (AFC) or anti-Müllerian hormone (AMH) to predict pregnancy or live birth. However, ESHRE do recommend using AFC or AMH for predicting high and low response to ovarian stimulation. While Part A of the ESHRE guideline is not referred to in the NICE guidance, the expert working group agreed that overall these ESHRE recommendations do align with NICE recommendation 1.18.4 to use AMH measurement or AFC as predictors of ovarian response to inform clinical decision making and patient counselling about the likelihood of live birth following assisted conception.

Is the recommendation and underpinning evidence current? Things to consider include:	*Whether the recommendation is likely to change over time (for example, information and support recommendations are more likely to be static and the evidence may need to be less up to date, whereas a recent evidence base is likely to be more important for recommendations on diagnosis and management):* Currently, there is limited high quality evidence available in this area. The recommendations are based on the available evidence and expert consensus. *How recently were searches performed or updated for the underlying evidence base?* Literature searches for the ESHRE guideline were initially performed on 1 November 2018 and updated on 2 February 2025. The ESHRE guideline will be considered for revision in 2029. *Has there been a recent check that the recommendation is up to date?* The expert working group agreed that the relevant recommendations are up to date and in line with current clinical practice. *How recent evidence searches or checks need to be may depend on, for example, how fast-moving or high-volume the evidence base is:* NICE is not aware of any large clinical trials being conducted in this area that are publishing soon. *Is the recommendation based on evidence that would be considered of appropriate quality within the area of the review question?* The recommendations are informed by the available evidence and supported by expert consensus. Quality of the evidence was taken into consideration when drafting recommendations, and strength of the recommendations was influenced by evidence quality and certainty.
Was health economics (health economic studies, and/or an economic model) taken into account? If not, is the recommendation likely to be a low resource impact? [Ignore this question if health economics is not a relevant consideration for the recommendation, for example qualitative or signs and symptoms questions]	No health economic evaluation or formal analysis of cost-effectiveness was performed for the ESHRE guideline, and resource impact was only assessed ‘where relevant’. However, the expert working group agreed that none of the recommendations would have any major resource impact in UK settings.

If health inequality issues relevant to the recommendation were identified by the EHIA for the NICE guideline, does the committee think the recommendation is likely to adversely impact on the identified health inequality issues? If yes, are additional recommendations required to address the unmet need or should the committee develop their own recommendations?	It was noted that some aspects relating to trans men and non-binary people with female reproductive organs are not covered in the ESHRE guideline. In general, ESHRE recommendations are applicable to this population, but some aspects/considerations (for example, care and support for trans and non-binary people, transvaginal monitoring, need to pause gender-affirming hormones) are not covered. However, these aspects are not covered in the NICE guideline either as it is expected that health professionals will exercise clinical judgement, and so no additional recommendations were developed. It was also noted that ESHRE guidance is not easily understandable or accessible for patients. This may be due to the lack of patient or patient representatives' involvement when drafting the guidance. However, a patient version of the guideline is available.
Is the recommendation likely to be acceptable to the NHS and / or social care services? Things to consider include:	*Population(s) in the evidence base for the source recommendation vs the target population of the NICE recommendation:* The population in the recommendations is broadly the same target population as the NICE recommendations. *Patient/service user views and preferences:* It appears that no patient or patient representatives' views were sought during the development of the ESHRE guideline, although a patient version of the ESHRE guideline is available. A patient representative member of the NICE guideline committee was present during the ESHRE cross-reference discussion, and they agreed that patients may find the ESHRE guidance difficult to understand, but that the patient version of the guideline would aid implementation and understanding. *Constraints, organisational barriers, legislation, policy, or any other issues that could impede implementation:* There are no anticipated constraints or barriers as the recommendations are reflective of current clinical practice. *Compatibility with cultures and values:* We do not anticipate there to be any issues of compatibilities with cultures and values.