National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

[E] Ovulation induction strategies for hypogonadotropic hypogonadism

NICE guideline NG257

Evidence reviews underpinning recommendations 1.30.1 and 1.30.2 in the NICE guideline

March 2026

Final

Developed by NICE

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Contents

Ovulation induction strategies for hypogonadotropic hypogonadism

Review question

What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Introduction

Ovulation requires the action of the following cascade of hormones: gonadotrophin-releasing hormone from the hypothalamus acts on the pituitary gland leading to the release of the gonadotrophins, luteinising hormone and follicle-stimulating hormone. These in turn act on the ovaries promoting the processes that lead to the release of an egg.

Defects at any level in this cascade can lead to reduced or absent ovulation, causing subfertility. If this occurs due to a defect at the level of the hypothalamus or pituitary gland, the condition is called hypogonadotropic hypogonadism. This failure of the hypothalamic-pituitary axis can result from a congenital defect or acquired causes including surgery, injury, tumour, infection, radiation, excessive weight loss and excessive exercise.

Based on the principle that a condition caused by a lack of hormones can be treated by hormone replacement, the treatment for hypogonadotropic hypogonadism can include replacement of the gonadotrophin-releasing hormone, gonadotrophins or, if applicable, by reducing excessive exercise and normalising weight where those are thought to be the cause. In recent years, the use of recombinant luteinising hormone and follicle-stimulating hormone has increased.

Therefore, aim of this review was to identify if there is new evidence for the optimal ovulation induction treatments in female factor fertility problem associated with hypogonadotropic hypogonadism.

Summary of the protocol

See Table 1: Summary of the protocol (PICO table)

for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Inclusion: People with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism Exclusion: People presenting with primary or secondary amenorrhea due to other causes will not be included in this review. If some, but not all, of a study's participants are eligible for the review, then a study will be included if at least 80% of its participants are eligible for this review
Intervention	• Interventions aimed at normalising weight and/or promoting exercise • Pulsatile gonadotrophin-releasing hormone (GnRH) ('GnRH pump') • Gonadotrophins Studies will be included that use ovulation induction strategies followed by natural intercourse, timed intercourse, or intrauterine insemination. Studies in people undergoing IVF/ICSI will be excluded from this review.
Comparison	• Trials comparing at least 2 of the above interventions • No treatment • Placebo
Outcome	**Critical** • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks; multiple births will be counted as 1 live birth event) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least 1 fetal heartbeat) The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised **Important** • Miscarriage (loss of a baby before 24 weeks gestational age) • Multiple gestation (defined as an ultrasound scan that has shown at least 2 fetal heartbeats) • Ovarian Hyperstimulation Syndrome (OHSS)

GnRH: gonadotropin hormone-releasing hormone; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilisation; OHSS: ovarian hyperstimulation syndrome.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

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

Effectiveness evidence

Included studies

One randomised controlled trial (RCT) was included for this review (Carone 2012). This RCT compared highly purified human menopausal gonadotropin (hMG-HP) to human recombinant follicle stimulation hormone (r-hFSH) plus human recombinant luteinizing hormone (r-hLH) for people with hypogonadotropic hypogonadism.

The included study is summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summary of the study that was included in this review is presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Carone 2012 RCT Italy	N=35 Participants with WHO type I hypogonadotropic anovulation (diagnosed with hypogonadotropic hypogonadism according to a negative P4 challenge test) Mean (SD) age in years: 30.39 (15.26)	hMG-HP 150 IU hMG-HP daily, as 150 IU FSH + 150 IU LH like activity Participants received gonadotropin treatment for ≤16 days and ovulation was induced by a single administration of hCG on the day after the last hMG-HP when the leading follicle had reached a mean diameter of ≥17 mm	r-hFSH/r-hLH 150 IU r-hFSH and 75 IU r-hLH daily Participants received gonadotropin treatment for ≤16 days and ovulation was induced by a single administration of hCG on the day after the last r-hFSH/r-hLH when the leading follicle had reached a mean diameter of ≥17 mm	• Live birth • Clinical pregnancy • Miscarriage • Multiple gestation • Ovarian Hyperstimulation Syndrome	N=30 participants had primary amenorrhea (85.7%) and N=5 participants (14.3%) had secondary amenorrhea Participants were treated for 1 cycle (series A). Those who did not become pregnant during the first cycle were optionally treated for a further 1 or 2 cycles (series B and C respectively) according to the same randomised groups

FSH: follicle stimulating hormone; hCG: human chorionic gonadotrophin; hMG-HP: highly purified human menopausal gonadotropin; IU: international unit; LH: luteinizing hormone; NR: not reported; RCT: randomised controlled trial; r-hFSH/r-hLH: human recombinant follicle stimulating hormone/human recombinant luteinizing hormone; SD: standard deviation; WHO: world health organisation.

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

Low quality evidence from 1 randomised clinical trial (RCT) showed no clinically important difference in live birth in people with hypogonadotropic hypogonadism taking highly purified human menopausal gonadotropin (hMG-HP) compared to human recombinant follicle stimulation hormone (r-hFSH)/human recombinant luteinizing hormone (r-hLH). However, this outcome was only reported at the end of the first cycle (series A).

Low or very low quality evidence from the same RCT showed a higher rate of clinical pregnancy for people receiving r-hFSH/r-hLH compared to hMG-HP at the end of the first cycle (series A) and all cycles combined (series A, B and C) when the outcome was both analysed according to the number of participants and the number of cycles. No clinically important differences between groups were shown in clinical pregnancy when the outcome was analysed at the end of the second cycle (series B) and the third cycle (series C), indicating that the differences between groups were largely driven by the first cycle (very low quality evidence).

Very low quality evidence showed no clinically important differences were in miscarriage, multiple gestation, or ovarian hyperstimulation syndrome in people taking hMG-HP compared to r-hFSH/r-hLH.

See appendix F for full GRADE tables.

Economic evidence

A total of 133 studies were identified in the health economic literature search for this review question. After duplicates were removed, 104 studies were screened on title and abstract. Of these 104 studies, 103 were excluded and one was included in this evidence review.

Included studies

One economic study was identified which was relevant to this question (Papaleo 2014).

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

See Table 3 for the economic evidence profile of the included study.

Table 3: Economic evidence profile of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectivenss	
Papaleo 2014	Potentially serious limitations[1,2,3,4]	Partially applicable[5,6]	Study employed a Markov decision-analytic model with a time horizon of 3 treatment cycles (<1 year)	€733	0.337 Clinical pregnancies[7]	€2,007 per additional clinical pregnancy	Probabilistic sensitivity analysis suggested recombinant gonadotrophin therapy was likely to be more costly and more effective than urinary gonadotrophin therapy

[1] *Healthy live birth rather than clinical pregnancy is true outcome of interest as a clinical pregnancy does not equate to a live birth*
[2] *Probabilistic sensitivity analysis undertaken but parameters for distributions not specified*
[3] *Industry funded*
[4] *The analysis may not have included all relevant comparators and therefore the evaluation only assesses the relative cost-effectiveness of the 2 interventions studied and not whether they represent a cost-effective use of resources more generally*
[5] *Setting was Italian National Health Service and a cost year of 2013*
[6] *QALYs not used to quantify health benefits and no cost-effectiveness threshold available for the outcome of clinical pregnancy*
[7] *Clinical pregnancy, as defined by the study, is defined as falling pregnant within the study time horizon*

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation as the population covered by this review is relatively small and it was not anticipated that recommendations would have a significant resource impact.

Unit costs

Resource	Unit costs	Source
Pergoveris: 150 IU r-hFSH + 75 IU r-hLH	£72.35	BNF Accessed 01/09/2023
Menopur: hMG-HP (150 IU)	£36.04	BNF Accessed 01/09/2023

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Live birth and clinical pregnancy rates were prioritised as critical outcomes by the committee. They were selected as the best indicators of fertility and were specified in the core outcome set for fertility research (Duffy 2020).

Miscarriage, multiple gestation, and ovarian hyperstimulation syndrome (OHSS) were identified as important outcomes by the committee. Miscarriage was prioritised as an important outcome as it provides meaningful information about the success of a pregnancy and can have a significant impact on the woman's psychological and physical health. Multiple gestation was prioritised as an important outcome as it can arise due to ovulation induction leading to the release of multiple eggs and results in a riskier pregnancy and birth for the mother and baby. The committee prioritised OHSS as an important outcome as it can occur in people undergoing ovulation induction, resulting in significant pain, and in severe cases the need for additional treatment and hospitalisation.

The quality of the evidence

The quality of the evidence was assessed with GRADE and rated as low and very low quality.

The evidence was downgraded for risk of bias (due to lack of information about concealment of the allocation sequence, absence of any blinding, and only participants who were unsuccessful in the first cycle and wished to continue with treatment were included in subsequent cycle analyses). The evidence was also downgraded for imprecision due to the 95% confidence interval crossing one or two thresholds for minimally important difference and due to a low number of events (less than 150). The evidence was not downgraded for indirectness, inconsistency, or publication bias.

Benefits and harms

The committee discussed the evidence for highly purified human menopausal gonadotropin (hMG-HP) compared to human recombinant follicle stimulation hormone (r-hFSH) plus human recombinant luteinizing hormone (r-hLH) and noted there was no important difference in live births in people with hypogonadotropic hypogonadism. The committee agreed that live birth was the most reliable and accurate indicator of fertility and so this indicated a lack of difference between the two preparations.

The committee discussed the higher rate of clinical pregnancy for those receiving r-hFSH/r-hLH compared to hMG-HP at the end of the first cycle (series A) and all cycles combined (series A, B and C) when this outcome was analysed according to the number of participants and number of cycles. However, they noted that the study was very small and was conducted in Italy where the use of r-hFSH/r-hLH may be more common in clinical practice than in the United Kingdom, where other formulations of gonadotrophins (such as hMG-HP) are used more frequently. Based on this evidence the committee agreed that it was not appropriate to recommend one gonadotrophin preparation over another.

The committee noted the absence of any RCT evidence comparing gonadotrophins to placebo or no treatment for ovulation induction for people with hypogonadotropic hypogonadism but emphasised that the chances of pregnancy without treatment would be negligible, as ovulation is required for a spontaneous pregnancy to occur. The committee highlighted that it is standard good clinical practice to offer gonadotrophins to people with hypogonadotropic hypogonadism to address the absent or decreased function of the gonads and made a recommendation in line with this. The committee agreed to leave the choice of gonadotrophin preparation and delivery format as a decision to be made by individual clinicians or centres.

The committee noted the absence of any eligible evidence on interventions aimed at normalising weight and/or exercise. Based on their clinical knowledge and experience, the committee agreed that increasing body weight for those with a low body mass index (BMI) and moderating exercise levels for those who undertake high levels of exercise, would improve the chance of regular ovulation, conception, and an uncomplicated pregnancy for people with hypogonadotropic hypogonadism and agreed to retain the recommendation from the previous guideline. The BMI cut-offs in the previous guideline were modified in line with current National Health Service (NHS) definitions of a healthy BMI which is between 18.5 and 24.9 kg/m^2. The committee discussed whether to make a research recommendation relating to weight and exercise but agreed that this was standard clinical practice and further research was unlikely to change practice, so did not prioritise this topic for a research recommendation.

The committee discussed that people who struggle to gain weight on their own may benefit from professional dietary support. However, in the absence of any evidence specific to this population and considering lengthy waiting times to see dieticians, the committee agreed that it was not appropriate to strengthen this recommendation beyond the offering of advice. They noted that there was advice on the NHS website about healthy ways to gain weight and so cross-referred to this.

The committee agreed that the previous guideline recommendations on monitoring ovulation induction during gonadotrophin therapy were still relevant and did not require changes.

Cost effectiveness and resource use

The committee discussed one study (Papaleo 2014) which found, using a Markov decision analytic approach, that the incremental cost-effectiveness ratio (ICER) of human recombinant follicle stimulation hormone (r-hFSH) relative to human recombinant luteinizing hormone (r-hLH) was €2,007 per clinical pregnancy. Although the committee noted that there was no cost-effectiveness threshold for such an outcome, they thought in the context of assisted reproductive technology, more generally, that this would represent a cost-effective use of resources if taken at face value. However, the committee noted that the study was rated as only partially applicable and as having serious limitations. They also noted that the primary purpose of the review had not been to compare different gonadotrophin preparations, and they did not think cost-effective recommendations could be made, based on this analysis.

The committee noted that it is standard good clinical practice to offer gonadotrophins to people with hypogonadotropic hypogonadism to address the absent or decreased function of

the gonads. The committee therefore made a recommendation aligning to best clinical practice – noting that the chances of pregnancy without treatment would be close to zero.

It is possible there may be a small increase in costs for the NHS if there is an increased uptake in the number of people receiving gonadotropins. However, hypogonadotropic hypogonadism is a relatively rare condition, and only a small proportion of this population will be looking to conceive. Therefore, as the cost of treatment is between £36.04 and £72.35 – any increased uptake of gonadotropins for people with hypogonadotropic hypogonadism is unlikely to lead to a significant resource impact.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.30.1 and 1.30.2.

References – included studies

Effectiveness

Carone 2012

Carone, D, Caropreso, C, Vitti, A et al. (2012) Efficacy of different gonadotropin combinations to support ovulation induction in WHO type I anovulation infertility: clinical evidences of human recombinant FSH/human recombinant LH in a 2:1 ratio and highly purified human menopausal gonadotropin stimulation protocols. Journal of endocrinological investigation 35(11): 996-1002

Economic

Papaleo E, Alviggi C, Colombo GL, Pisanelli C, Ripellino C, Longobardi S, Canonico PL. Cost-effectiveness analysis on the use of rFSH + rLH for the treatment of anovulation in hypogonadotropic hypogonadal women. Therapeutics and Clinical Risk Management. 2014 Jun 25; 10:479-84.

Other

Duffy 2020

Duffy JM, AlAhwany H, Bhattacharya S, Collura B, Curtis C, Evers JL, Farquharson RG, Franik S, Giudice LC, Khalaf Y, Knijnenburg JM. (2020) Developing a core outcome set for future infertility research: an international consensus development study. Human Reproduction 35(12): 2725-34.

Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023454807
1.	Review title	Clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism
2.	Review question	What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?
3.	Objective	To determine the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism
4.	Searches	The following databases will be searched (from 2011 [the date of the last search for the NICE Fertility guideline] to the date of the search): • Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be restricted by:

ID	Field	Content
		• English language • Human studies The guideline committee will decide whether and when to re-run the searches before final submission of the review to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Treatments for female factor fertility problems associated with hypogonadotropic hypogonadism
6.	Population	Inclusion: • People with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism Exclusion: • People presenting with primary or secondary amenorrhea due to other causes will not be included in this review. If some, but not all, of a study's participants are eligible for the review, then a study will be included if at least 80% of its participants are eligible for this review.
7.	Interventions	• Interventions aimed at normalising weight and/or promoting exercise • Pulsatile gonadotrophin-releasing hormone (GnRH) ('GnRH pump') • Gonadotrophins Studies will be included that use ovulation induction strategies followed by natural intercourse, timed intercourse, or intrauterine insemination. Studies in people undergoing IVF/ICSI will be excluded from this review.
8.	Comparators	• Trials comparing at least 2 of the above interventions • No treatment • Placebo
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs* (individual or cluster) • If no RCT evidence: ○ Quasi-randomised controlled trials (experimental studies using a non-randomly assigned control group design with matched comparison or another method of controlling for confounding variables)

ID	Field	Content
		*Cross-over RCTs will be included but only where data can be extracted for the end of the first phase
10.	Other exclusion criteria	• Other exclusion criteria: • Language limitations: non-English-language papers will be excluded (unless data can be obtained, and risk of bias assessed, from an existing systematic review) • Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted (and risk of bias assessed) from elsewhere (for instance, from an existing systematic review)
11.	Context	This guidance will update and replace the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
12.	Primary outcomes (critical outcomes)	• Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks; multiple births will be counted as 1 live birth event) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least 1 fetal heartbeat) The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised
13.	Secondary outcomes (important outcomes)	• Miscarriage (loss of a baby before 24 weeks gestational age) • Multiple gestation (defined as an ultrasound scan that has shown at least 2 fetal heartbeats) • Ovarian Hyperstimulation Syndrome (OHSS)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions, setting and follow-up,

ID	Field	Content
		relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where there is available data, meta-analyses will be conducted using Cochrane Review Manager software, and data will be presented as risk ratios or odds ratios (all included outcomes are dichotomous outcomes). It is considered likely that a random-effects model will be used for meta-analyses (based on assumptions about methodological diversity of studies). Funnel plot asymmetry (relationship between the magnitude of the effect estimate and study size) will be considered (for meta-analyses that include at least 10 studies), and where asymmetry is indicated a fixed-effects model will be conducted (and both random-effects and fixed-effects analyses will be presented) or sensitivity analyses excluding small studies will be considered. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: ○ Live birth: statistical significance ○ Dichotomous outcomes (other than live birth): 0.8 and 1.25 for all other relative dichotomous outcomes
17.	Analysis of sub-groups	Evidence will be sub-grouped by the following: • Age (based on the mean age reported in the study):

ID	Field	Content		
		○ ≤35 years ○ >35 years Where evidence is subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	June 2023		
22.	Anticipated completion date	November 2024		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	x
		Piloting of the study selection process	☐	x
		Formal screening of search results against eligibility criteria	☐	x

ID	Field	Content		
		Data extraction	☐	x
		Risk of bias (quality) assessment	☐	x
		Data analysis	☐	x
24.	Named contact	5a. Named contact Guideline Development Team A 5b. Named contact e-mail FertilityProblems@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team A, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Senior Technical Analyst • Technical Analyst		
26.	Funding sources/sponsor	This systematic review is being completed by NICE		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263		
29.	Other registration details	None		

ID	Field	Content	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=454807	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Female factor fertility problems, infertility, ovulation induction, hypogonadotropic hypogonadism	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Database: Ovid MEDLINE(R) ALL <1946 to August 01, 2023>

Date of last search: 02/08/2023

#	Searches
1	Hypogonadism/ or Kallmann Syndrome/
2	(hypogonadotro* adj4 (hypogonadism or anovulation)).tw.
3	((gonadal or GnRH or gonadotrop?in releasing hormone) adj4 (failure* or inadequate* or abnormal* or deficien* or deficit? or defect*)).tw.
4	(secondary hypogonadism or hypogonadotrop?ism or kallman* syndrome).tw.
5	or/1-4
6	exp Ovulation Induction/
7	(ovulat* adj1 (induc* or stimulat* or increas* or treatment* or therap*)).tw.
8	Fertility Agents/ or Fertility Agents, Female/
9	Gonadotropins/
10	exp Gonadotropins, Pituitary/
11	(gonadotrophin* or gonadotropi* or gonad stimulat*).tw.
12	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or folliculo-stimulating or pituitary) adj2 hormone*).tw.
13	(lutropin adj1 (alpha or alfa)).tw.
14	(LH or rLH or lhfshrh or lfrh or lhfsh or FSH or rFSH or recFSH).tw.
15	(urinary adj1 follicle?).tw.
16	(anthrogon or puregon or metrodin or follitropin* or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17).tw.
17	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
18	(Menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp-90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
19	(hMG or hMGhp or FSHhp or uFSH or rHLH or r-hFSH or rhFSH).tw.
20	exp Chorionic Gonadotropin/
21	(choriogonadotrop* or choriogonin or HCG or "h.c.g." or novarel or ovidrel or pregnyl or biogonadil or biogonadyl or chorulon or gonabion or "a.p.l." or apl or antuitrin-s or choragon or chorigon or chorex or choron or chorulon or coriantin or corion or endocorion or follutein or gestasol dry or gonacor or gonadex or gonadotropyl-c or gonatropin or homosten or ivf-c or libigen or ml-04a or ml04a or ovulgone or physex or praedyn or pranturon or predalon or pregnesin or primogonyl or profasi or promogonyl or prophasi or prymogonyl or pubergen or puberogen or riogon or synapoidin or zivafert).tw.
22	Gonadotropin-Releasing Hormone/
23	((GnRH or GnRHa or gn-rh) adj4 (puls* or pump* or infus* or perfus* or intravenous* or subcutaneous* or stimulat* or therap* or treatment* or inject* or administ*)).tw.
24	(33515-09-2 or 51952-41-1 or 52699-48-6 or cystorelin or dirigestran or factrel or gonadoliberin or gonadorelin or kryptocur or luliberin).tw.
25	exp Life Style/ or Health Promotion/
26	((lifestyle or life style) adj3 (change* or changing or adjust* or intervention* or modif* or restrict*)).tw.
27	(health* adj2 (life style or lifestyle or behavio?r* or promot*)).tw.
28	Exercise/ or Exercise Therapy/ or Sports/
29	(exercise* or exercising or physical* activ* or fitness or train* or sport*).tw.
30	exp Diet Therapy/ or Diet/
31	(diet* adj4 (therap* or modif* or restrict* or balance* or healthy or interven* or change* or adjust* or behavio?r* or treatment*)).tw.

#	Searches
32	weight reduction programs/ or weight loss/ or weight gain/
33	((weight* or "body mass index" or "body mass indices" or "body fat index" or "body fat indexes" or "body fat indices" or BMI or BFI) adj1 (manage* or managing or regulat* or loss* or lose or reduc* or decreas* or gain* or increas* or optimiz* or optimis* or normalis* or normaliz*)).tw.
34	or/6-33
35	5 and 34
36	letter/
37	editorial/
38	news/
39	exp historical article/
40	Anecdotes as topic/
41	comment/
42	case reports/
43	(letter or comment*).ti.
44	or/36-43
45	randomized controlled trial/ or random*.ti,ab.
46	44 not 45
47	animals/ not humans/
48	exp Animals, Laboratory/
49	exp Animal Experimentation/
50	exp Models, Animal/
51	exp Rodentia/
52	(rat or rats or rodent* or mouse or mice).ti.
53	or/46-52
54	35 not 53
55	limit 54 to english language
56	limit 55 to ed=20110718-20230831
57	limit 55 to dt=20110718-20230831
58	56 or 57
59	meta-analysis/
60	meta-analysis as topic/
61	(meta analy* or metanaly* or metaanaly*).ti,ab.
62	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
63	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
64	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
65	(search* adj4 literature).ab.
66	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
67	cochrane.jw.
68	or/59-67
69	randomized controlled trial.pt.
70	controlled clinical trial.pt.
71	pragmatic clinical trial.pt.
72	randomi#ed.ab.
73	placebo.ab.
74	randomly.ab.
75	Clinical Trials as topic.sh.
76	trial.ti.
77	or/69-76
78	58 and (68 or 77)
79	Observational Studies as Topic/
80	Observational Study/
81	Epidemiologic Studies/

#	Searches
82	exp Case-Control Studies/
83	exp Cohort Studies/
84	Cross-Sectional Studies/
85	Controlled Before-After Studies/
86	Historically Controlled Study/
87	Interrupted Time Series Analysis/
88	Comparative Study.pt.
89	case control$.tw.
90	case series.tw.
91	(cohort adj (study or studies)).tw.
92	cohort analy$.tw.
93	(follow up adj (study or studies)).tw.
94	(observational adj (study or studies)).tw.
95	longitudinal.tw.
96	prospective.tw.
97	retrospective.tw.
98	cross sectional.tw.
99	or/79-98
100	58 and 99
101	100 not 78

Database: Embase <1974 to 2023 August 01>

Date of last search: 02/08/2023

#	Searches
1	hypogonadotropic hypogonadism/ or Kallmann syndrome/
2	(hypogonadotro* adj4 (hypogonadism or anovulation)).tw.
3	((gonadal or GnRH or gonadotrop?in releasing hormone) adj4 (failure* or inadequate* or abnormal* or deficien* or deficit? or defect*)).tw.
4	(secondary hypogonadism or hypogonadotrop?ism or kallman* syndrome).tw.
5	or/1-4
6	ovulation induction/
7	(ovulat* adj1 (induc* or stimulat* or increas* or treatment* or therap*)).tw.
8	fertility promoting agent/
9	gonadotropin/
10	(gonadotrophin* or gonadotropi* or gonad stimulat*).tw.
11	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or folliculo-stimulating or pituitary) adj2 hormone*).tw.
12	exp luteinizing hormone derivative/
13	exp follitropin derivative/
14	(lutropin adj1 (alpha or alfa)).tw.
15	(LH or rLH or lhfshrh or lfrh or lhfsh or FSH or rFSH or recFSH).tw.
16	(urinary adj1 follicle?).tw.
17	(anthrogon or puregon or metrodin or follitropin* or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17).tw.
18	human menopausal gonadotropin/
19	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
20	(Menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp-90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
21	(hMG or hMGhp or FSHhp or uFSH or rHLH or r-hFSH or rhFSH).tw.
22	exp chorionic gonadotropin derivative/

#	Searches
23	(choriogonadotrop* or choriogonin or HCG or "h.c.g." or novarel or ovidrel or pregnyl or biogonadil or biogonadyl or chorulon or gonabion or "a.p.l." or apl or antuitrin-s or choragon or chorigon or chorex or choron or chorulon or coriantin or corion or endocorion or follutein or gestasol dry or gonacor or gonadex or gonadotropyl-c or gonatropin or homosten or ivf-c or libigen or ml-04a or ml04a or ovulgone or physex or praedyn or pranturon or predalon or pregnesin or primogonyl or profasi or promogonyl or prophasi or prymogonyl or pubergen or puberogen or riogon or synapoidin or zivafert).tw.
24	exp gonadorelin derivative/
25	((GnRH or GnRHa or gn-rh) adj4 (puls* or pump* or infus* or perfus* or intravenous* or subcutaneous* or stimulat* or therap* or treatment* or inject* or administ*)).tw.
26	(33515-09-2 or 51952-41-1 or 52699-48-6 or cystorelin or dirigestran or factrel or gonadoliberin or gonadorelin or kryptocur or luliberin).tw.
27	exp lifestyle/ or lifestyle modification/ or health promotion/
28	((lifestyle or life style) adj3 (change* or changing or adjust* or intervention* or modif* or restrict*)).tw.
29	(health* adj2 (life style or lifestyle or behavio?r* or promot*)).tw.
30	exercise/ or physical activity/ or kinesiotherapy/ or fitness/ or sport/
31	(exercise* or exercising or physical* activ* or fitness or train* or sport*).tw.
32	exp diet therapy/ or diet/ or healthy diet/
33	(diet* adj4 (therap* or modif* or restrict* or balance* or healthy or interven* or change* or changing or adjust* or behavio?r* or treatment*)).tw.
34	weight loss program/ or body weight loss/ or body weight gain/
35	((weight* or "body mass index" or "body mass indices" or "body fat index" or "body fat indexes" or "body fat indices" or BMI or BFI) adj1 (manage* or managing or regulat* or loss* or lose or reduc* or decreas* or gain* or increas* or optimiz* or optimis* or normalis* or normaliz*)).tw.
36	or/6-35
37	5 and 36
38	letter.pt. or letter/
39	note.pt.
40	editorial.pt.
41	case report/ or case study/
42	(letter or comment*).ti.
43	or/38-42
44	randomized controlled trial/ or random*.ti,ab.
45	43 not 44
46	animal/ not human/
47	nonhuman/
48	exp Animal Experiment/
49	exp Experimental Animal/
50	animal model/
51	exp Rodent/
52	(rat or rats or rodent* or mouse or mice).ti.
53	or/45-52
54	37 not 53
55	limit 54 to english language
56	limit 55 to dc=20110718-20230831
57	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
58	56 not 57
59	systematic review/
60	meta-analysis/
61	(meta analy* or metanaly* or metaanaly*).ti,ab.
62	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
63	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
64	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
65	(search* adj4 literature).ab.
66	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.

#	Searches
67	((pool* or combined) adj2 (data or trials or studies or results)).ab.
68	cochrane.jw.
69	or/59-68
70	random*.ti,ab.
71	factorial*.ti,ab.
72	(crossover* or cross over*).ti,ab.
73	((doubl* or singl*) adj blind*).ti,ab.
74	(assign* or allocat* or volunteer* or placebo*).ti,ab.
75	crossover procedure/
76	single blind procedure/
77	randomized controlled trial/
78	double blind procedure/
79	or/70-78
80	58 and (69 or 79)
81	Clinical study/
82	Case control study/
83	Family study/
84	Longitudinal study/
85	Retrospective study/
86	comparative study/
87	Prospective study/
88	Randomized controlled trials/
89	87 not 88
90	Cohort analysis/
91	cohort analy$.tw.
92	(Cohort adj (study or studies)).tw.
93	(Case control$ adj (study or studies)).tw.
94	(follow up adj (study or studies)).tw.
95	(observational adj (study or studies)).tw.
96	(epidemiologic$ adj (study or studies)).tw.
97	(cross sectional adj (study or studies)).tw.
98	case series.tw.
99	prospective.tw.
100	retrospective.tw.
101	or/81-86,89-100
102	58 and 101
103	102 not 80

Database: Cochrane Database of Systematic Reviews Issue 8 of 12, August 2023

Date of last search: 02/08/2023

#	Searches
#1	MeSH descriptor: [Hypogonadism] this term only
#2	MeSH descriptor: [Kallmann Syndrome] this term only
#3	(hypogonadotro* near/4 (hypogonadism or anovulation)):ti,ab
#4	((gonadal or GnRH or "gonadotropin releasing hormone" or "gonadotrophin releasing hormone") near/4 (failure* or inadequate* or abnormal* or deficien* or deficit* or defect*)):ti,ab
#5	("secondary hypogonadism" or hypogonadotropism or hypogonadotrophism or (kallman* next syndrome)):ti,ab
#6	{or #1-#5}
#7	MeSH descriptor: [Ovulation Induction] explode all trees
#8	(ovulat* near/1 (induc* or stimulat* or increas* or treatment* or therap*)):ti,ab
#9	MeSH descriptor: [Fertility Agents] this term only
#10	MeSH descriptor: [Fertility Agents, Female] this term only

#	Searches
#11	MeSH descriptor: [Gonadotropins] this term only
#12	MeSH descriptor: [Gonadotropins, Pituitary] explode all trees
#13	(gonadotrophin* or gonadotropi* or (gonad next stimulat*)):ti,ab
#14	(("interstitial cell-stimulating" or luteinising or luteinizing or "follicle stimulating" or folliculostimulating or folliculo-stimulating or pituitary) near/2 hormone*):ti,ab
#15	(lutropin near/1 (alpha or alfa)):ti,ab
#16	(LH or rLH or lhfshrh or lfrh or lhfsh or FSH or rFSH or recFSH):ti,ab
#17	(urinary near/1 follicle*):ti,ab
#18	(anthrogon or puregon or metrodin or follitropin* or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17):ti,ab
#19	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon):ti,ab
#20	(Menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp-90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex):ti,ab
#21	(hMG or hMGhp or FSHhp or uFSH or rHLH or r-hFSH or rhFSH):ti,ab
#22	MeSH descriptor: [Chorionic Gonadotropin] explode all trees
#23	(choriogonadotrop* or choriogonin or HCG or "h.c.g." or novarel or ovidrel or pregnyl or biogonadil or biogonadyl or chorulon or gonabion or "a.p.l." or apl or antuitrin-s or choragon or chorigon or chorex or choron or chorulon or coriantin or corion or endocorion or follutein or "gestasol dry" or gonacor or gonadex or gonadotropyl-c or gonatropin or homosten or ivf-c or libigen or ml-04a or ml04a or ovulgone or physex or praedyn or pranturon or predalon or pregnesin or primogonyl or profasi or promogonyl or prophasi or prymogonyl or pubergen or puberogen or riogon or synapoidin or zivafert):ti,ab
#24	MeSH descriptor: [Gonadotropin-Releasing Hormone] this term only
#25	((GnRH or GnRHa or gn-rh) near/4 (puls* or pump* or infus* or perfus* or intravenous* or subcutaneous* or stimulat* or therap* or treatment* or inject* or administ*)):ti,ab
#26	("33515-09-2" or "51952-41-1" or "52699-48-6" or cystorelin or dirigestran or factrel or gonadoliberin or gonadorelin or kryptocur or luliberin):ti,ab
#27	MeSH descriptor: [Life Style] explode all trees
#28	MeSH descriptor: [Health Promotion] this term only
#29	((lifestyle or "life style") near/3 (change* or changing or adjust* or intervention* or modif* or restrict*)):ti,ab
#30	(health* near/2 ("life style" or lifestyle or behaviour* or behavior* or promot*)):ti,ab
#31	MeSH descriptor: [Exercise] this term only
#32	MeSH descriptor: [Exercise Therapy] this term only
#33	MeSH descriptor: [Sports] this term only
#34	(exercise* or exercising or (physical* next activ*) or fitness or train* or sport*):ti,ab
#35	MeSH descriptor: [Diet Therapy] explode all trees
#36	MeSH descriptor: [Diet] this term only
#37	(diet* near/4 (therap* or modif* or restrict* or balance* or healthy or interven* or change* or changing or adjust* or behaviour* or behavior* or treatment*)):ti,ab
#38	MeSH descriptor: [Weight Reduction Programs] this term only
#39	MeSH descriptor: [Weight Loss] this term only
#40	MeSH descriptor: [Weight Gain] this term only
#41	((weight* or "body mass index" or "body mass indices" or "body fat index" or "body fat indexes" or "body fat indices" or BMI or BFI) near/1 (manage* or managing or regulat* or loss* or lose or reduc* or decreas* or gain* or increas* or optimiz* or optimis* or normalis* or normaliz*)):ti,ab
#42	{or #7-#41}
#43	#6 and #42
#44	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#45	#43 not #44
#46	"conference":pt
#47	#45 not #46 with Cochrane Library publication date Between Jul 2011 and Aug 2023, in Cochrane Reviews

Database: Cochrane Central Register of Controlled Trials Issue 7 of 12, July 2023

Date of last search: 02/08/2023

#	Searches
#1	MeSH descriptor: [Hypogonadism] this term only
#2	MeSH descriptor: [Kallmann Syndrome] this term only
#3	(hypogonadotro* near/4 (hypogonadism or anovulation)):ti,ab
#4	((gonadal or GnRH or "gonadotropin releasing hormone" or "gonadotrophin releasing hormone") near/4 (failure* or inadequate* or abnormal* or deficien* or deficit? or defect*)):ti,ab
#5	("secondary hypogonadism" or hypogonadotropism or hypogonadotrophism or (kallman* next syndrome)):ti,ab
#6	{or #1-#5}
#7	MeSH descriptor: [Ovulation Induction] explode all trees
#8	(ovulat* near/1 (induc* or stimulat* or increas* or treatment* or therap*)):ti,ab
#9	MeSH descriptor: [Fertility Agents] this term only
#10	MeSH descriptor: [Fertility Agents, Female] this term only
#11	MeSH descriptor: [Gonadotropins] this term only
#12	MeSH descriptor: [Gonadotropins, Pituitary] explode all trees
#13	(gonadotrophin* or gonadotropi* or (gonad next stimulat*)):ti,ab
#14	(("interstitial cell-stimulating" or luteinising or luteinizing or "follicle stimulating" or folliculostimulating or folliculo-stimulating or pituitary) near/2 hormone*):ti,ab
#15	(lutropin near/1 (alpha or alfa)):ti,ab
#16	(LH or rLH or lhfshrh or lfrh or lhfsh or FSH or rFSH or recFSH):ti,ab
#17	(urinary near/1 follicle*):ti,ab
#18	(anthrogon or puregon or metrodin or follitropin* or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17):ti,ab
#19	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon):ti,ab
#20	(Menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp-90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex):ti,ab
#21	(hMG or hMGhp or FSHhp or uFSH or rHLH or r-hFSH or rhFSH):ti,ab
#22	MeSH descriptor: [Chorionic Gonadotropin] explode all trees
#23	(choriogonadotrop* or choriogonin or HCG or "h.c.g." or novarel or ovidrel or pregnyl or biogonadil or biogonadyl or chorulon or gonabion or "a.p.l." or apl or antuitrin-s or choragon or chorigon or chorex or choron or chorulon or coriantin or corion or endocorion or follutein or "gestasol dry" or gonacor or gonadex or gonadotropyl-c or gonatropin or homosten or ivf-c or libigen or ml-04a or ml04a or ovulgone or physex or praedyn or pranturon or predalon or pregnesin or primogonyl or profasi or promogonyl or prophasi or prymogonyl or pubergen or puberogen or riogon or synapoidin or zivafert):ti,ab
#24	MeSH descriptor: [Gonadotropin-Releasing Hormone] this term only
#25	((GnRH or GnRHa or gn-rh) near/4 (puls* or pump* or infus* or perfus* or intravenous* or subcutaneous* or stimulat* or therap* or treatment* or inject* or administ*)):ti,ab
#26	("33515-09-2" or "51952-41-1" or "52699-48-6" or cystorelin or dirigestran or factrel or gonadoliberin or gonadorelin or kryptocur or luliberin):ti,ab
#27	MeSH descriptor: [Life Style] explode all trees
#28	MeSH descriptor: [Health Promotion] this term only
#29	((lifestyle or "life style") near/3 (change* or changing or adjust* or intervention* or modif* or restrict*)):ti,ab
#30	(health* near/2 ("life style" or lifestyle or behaviour* or behavior* or promot*)):ti,ab
#31	MeSH descriptor: [Exercise] this term only
#32	MeSH descriptor: [Exercise Therapy] this term only
#33	MeSH descriptor: [Sports] this term only
#34	(exercise* or exercising or (physical* next activ*) or fitness or train* or sport*):ti,ab
#35	MeSH descriptor: [Diet Therapy] explode all trees
#36	MeSH descriptor: [Diet] this term only
#37	(diet* near/4 (therap* or modif* or restrict* or balance* or healthy or interven* or change* or changing or adjust* or behaviour* or behavior* or treatment*)):ti,ab
#38	MeSH descriptor: [Weight Reduction Programs] this term only
#39	MeSH descriptor: [Weight Loss] this term only

#	Searches
#40	MeSH descriptor: [Weight Gain] this term only
#41	((weight* or "body mass index" or "body mass indices" or "body fat index" or "body fat indexes" or "body fat indices" or BMI or BFI) near/1 (manage* or managing or regulat* or loss* or lose or reduc* or decreas* or gain* or increas* or optimiz* or optimis* or normalis* or normaliz*)):ti,ab
#42	{or #7-#41}
#43	#6 and #42
#44	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#45	#43 not #44
#46	"conference":pt
#47	#45 not #46 with Publication Year from 2011 to 2023, in Trials

Database: Epistemonikos

Date of last search: 02/08/2023

Search 1:

#	Searches
1	((hypogonadotro* AND (hypogonadism or anovulation)) OR ((gonadal OR GnRH OR "gonadotropin releasing hormone" OR "gonadotrophin releasing hormone" OR "gonadotropin-releasing hormone" OR "gonadotrophin-releasing hormone") AND (failure OR inadequa* OR abnormal* OR deficien* OR deficit* OR defect*)) OR "secondary hypogonadism" OR hypogonadotropism OR hypogonadotrophism OR "kallman syndrome" OR "kallmans syndrome" OR "kallmann syndrome" OR "kallmanns syndrome")
	AND
1	((ovulat* AND (induc* OR stimulat* OR increas* OR treatment* OR therap*)) OR gonadotrophin* OR gonadotropi* OR (gonad* AND stimulat*) OR (("interstitial cell-stimulating" OR "interstitial cell stimulating" OR luteinising OR luteinizing OR "follicle stimulating" OR folliculostimulating OR folliculo-stimulating OR pituitary) AND hormone*) OR (lutropin AND (alpha OR alfa)) OR LH OR rLH OR lhfshrh OR lfrh OR lhfsh OR FSH OR rFSH OR recFSH OR "urinary follicle" OR "urinary follicles" OR OR hMG OR hMGhp OR FSHhp OR uFSH OR rHLH OR r-hFSH OR "r hFSH" OR rhFSH OR HCG OR ((GnRH OR GnRHa OR gn-rh OR "gn rh") AND (puls* OR pump* OR infus* OR perfus* OR intravenous* OR subcutaneous* OR stimulat* OR therap* OR treatment* OR inject* OR administ*)))
	1 AND 2
	Limit to systematic reviews

Search 2:

#	Searches
1	((hypogonadotro* AND (hypogonadism or anovulation)) OR ((gonadal OR GnRH OR "gonadotropin releasing hormone" OR "gonadotrophin releasing hormone" OR "gonadotropin-releasing hormone" OR "gonadotrophin-releasing hormone") AND (failure OR inadequa* OR abnormal* OR deficien* OR deficit* OR defect*)) OR "secondary hypogonadism" OR hypogonadotropism OR hypogonadotrophism OR "kallman syndrome" OR "kallmans syndrome" OR "kallmann syndrome" OR "kallmanns syndrome")
	AND
1	(((lifestyle OR "life style") AND (change* OR changing OR adjust* OR intervention* OR modif* OR restrict*)) OR (health* AND ("life style" OR lifestyle OR behaviour* OR behavior* OR promot*)) OR (exercise* OR exercising OR (physical* AND activ*) OR fitness OR train* OR sport*) OR (diet* AND (therap* OR modif* OR restrict* OR balance* OR healthy OR interven* OR change* OR changing OR adjust* OR behaviour* OR behavior* OR treatment*)) OR ((weight* OR "body mass index" OR "body mass indices" OR "body fat index" OR "body fat indexes" OR "body fat indices" OR BMI OR BFI) AND (manage* OR managing OR regulat* OR loss* OR lose OR reduc* OR decreas* OR gain* OR increas* OR optimiz* OR optimis* OR normalis* OR normaliz*)))
	1 AND 2
	Limit to systematic reviews

Health economic literature search strategies

Database: Ovid MEDLINE(R) ALL <1946 to August 02, 2023>

Date of last search: 03/08/2023

#	Searches
1	Hypogonadism/ or Kallmann Syndrome/
2	(hypogonadotro* adj4 (hypogonadism or anovulation)).tw.
3	((gonadal or GnRH or gonadotrop?in releasing hormone) adj4 (failure* or inadequate* or abnormal* or deficien* or deficit? or defect*)).tw.
4	(secondary hypogonadism or hypogonadotrop?ism or kallman* syndrome).tw.
5	or/1-4
6	exp Ovulation Induction/
7	(ovulat* adj1 (induc* or stimulat* or increas* or treatment* or therap*)).tw.
8	Fertility Agents/ or Fertility Agents, Female/
9	Gonadotropins/
10	exp Gonadotropins, Pituitary/
11	(gonadotrophin* or gonadotropi* or gonad stimulat*).tw.
12	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or folliculo-stimulating or pituitary) adj2 hormone*).tw.
13	(lutropin adj1 (alpha or alfa)).tw.
14	(LH or rLH or lhfshrh or lfrh or lhfsh or FSH or rFSH or recFSH).tw.
15	(urinary adj1 follicle?).tw.
16	(anthrogon or puregon or metrodin or follitropin* or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or puregon or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17).tw.
17	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
18	(Menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp-90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
19	(hMG or hMGhp or FSHhp or uFSH or rHLH or r-hFSH or rhFSH).tw.
20	exp Chorionic Gonadotropin/
21	(choriogonadotrop* or choriogonin or HCG or "h.c.g." or novarel or ovidrel or pregnyl or biogonadil or biogonadyl or chorulon or gonabion or "a.p.l." or apl or antuitrin-s or choragon or chorigon or chorex or choron or chorulon or coriantin or corion or endocorion or follutein or gestasol dry or gonacor or gonadex or gonadotropyl-c or gonatropin or homosten or ivf-c or libigen or ml-04a or ml04a or ovulgone or physex or praedyn or pranturon or predalon or pregnesin or primogonyl or profasi or promogonyl or prophasi or prymogonyl or pubergen or puberogen or riogon or synapoidin or zivafert).tw.
22	Gonadotropin-Releasing Hormone/
23	((GnRH or GnRHa or gn-rh) adj4 (puls* or pump* or infus* or perfus* or intravenous* or subcutaneous* or stimulat* or therap* or treatment* or inject* or administ*)).tw.
24	(33515-09-2 or 51952-41-1 or 52699-48-6 or cystorelin or dirigestran or factrel or gonadoliberin or gonadorelin or kryptocur or luliberin).tw.
25	exp Life Style/ or Health Promotion/
26	((lifestyle or life style) adj3 (change* or changing or adjust* or intervention* or modif* or restrict*)).tw.
27	(health* adj2 (life style or lifestyle or behavio?r* or promot*)).tw.
28	Exercise/ or Exercise Therapy/ or Sports/
29	(exercise* or exercising or physical* activ* or fitness or train* or sport*).tw.
30	exp Diet Therapy/ or Diet/
31	(diet* adj4 (therap* or modif* or restrict* or balance* or healthy or interven* or change* or adjust* or behavio?r* or treatment*)).tw.
32	weight reduction programs/ or weight loss/ or weight gain/
33	((weight* or "body mass index" or "body mass indices" or "body fat index" or "body fat indexes" or "body fat indices" or BMI or BFI) adj1 (manage* or managing or regulat* or loss* or lose or reduc* or decreas* or gain* or increas* or optimiz* or optimis* or normalis* or normaliz*)).tw.
34	or/6-33
35	5 and 34
36	letter/
37	editorial/
38	news/
39	exp historical article/

#	Searches
40	Anecdotes as topic/
41	comment/
42	case reports/
43	(letter or comment*).ti.
44	or/36-43
45	randomized controlled trial/ or random*.ti,ab.
46	44 not 45
47	animals/ not humans/
48	exp Animals, Laboratory/
49	exp Animal Experimentation/
50	exp Models, Animal/
51	exp Rodentia/
52	(rat or rats or rodent* or mouse or mice).ti.
53	or/46-52
54	35 not 53
55	limit 54 to english language
56	limit 55 to ed=20110125-20230831
57	limit 55 to dt=20110125-20230831
58	56 or 57
59	Economics/
60	Value of life/
61	exp "Costs and Cost Analysis"/
62	exp Economics, Hospital/
63	exp Economics, Medical/
64	exp Resource Allocation/
65	Economics, Nursing/
66	Economics, Pharmaceutical/
67	exp "Fees and Charges"/
68	exp Budgets/
69	budget*.ti,ab.
70	cost*.ti,ab.
71	(economic* or pharmaco?economic*).ti,ab.
72	(price* or pricing*).ti,ab.
73	(financ* or fee or fees or expenditure* or saving*).ti,ab.
74	(value adj2 (money or monetary)).ti,ab.
75	resourc* allocat*.ti,ab.
76	(fund or funds or funding* or funded).ti,ab.
77	(ration or rations or rationing* or rationed).ti,ab.
78	ec.fs.
79	or/59-78
80	quality-adjusted life years/
81	sickness impact profile/
82	(quality adj2 (wellbeing or well being)).ti,ab.
83	sickness impact profile.ti,ab.
84	disability adjusted life.ti,ab.
85	(qal* or qtime* or qwb* or daly*).ti,ab.
86	(euroqol* or eq5d* or eq 5*).ti,ab.
87	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
88	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
89	(hui or hui1 or hui2 or hui3).ti,ab.
90	(health* year* equivalent* or hye or hyes).ti,ab.
91	discrete choice*.ti,ab.

#	Searches
92	rosser.ti,ab.
93	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
94	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
95	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
96	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
97	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
98	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
99	or/80-98
100	58 and (79 or 99)

Database: Embase <1974 to 2023 August 02>

Date of last search: 03/08/2023

#	Searches
1	hypogonadotropic hypogonadism/ or Kallmann syndrome/
2	(hypogonadotro* adj4 (hypogonadism or anovulation)).tw.
3	((gonadal or GnRH or gonadotrop?in releasing hormone) adj4 (failure* or inadequate* or abnormal* or deficien* or deficit? or defect*)).tw.
4	(secondary hypogonadism or hypogonadotrop?ism or kallman* syndrome).tw.
5	or/1-4
6	ovulation induction/
7	(ovulat* adj1 (induc* or stimulat* or increas* or treatment* or therap*)).tw.
8	fertility promoting agent/
9	gonadotropin/
10	(gonadotrophin* or gonadotropi* or gonad stimulat*).tw.
11	((interstitial cell-stimulating or luteini?ing or follicle stimulating or folliculostimulating or folliculo-stimulating or pituitary) adj2 hormone*).tw.
12	exp luteinizing hormone derivative/
13	exp follitropin derivative/
14	(lutropin adj1 (alpha or alfa)).tw.
15	(LH or rLH or lhfshrh or lfrh or lhfsh or FSH or rFSH or recFSH).tw.
16	(urinary adj1 follicle?).tw.
17	(anthrogon or puregon or metrodin or follitropin* or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or puregon or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17).tw.
18	human menopausal gonadotropin/
19	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
20	(Menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp-90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
21	(hMG or hMGhp or FSHhp or uFSH or rHLH or r-hFSH or rhFSH).tw.
22	exp chorionic gonadotropin derivative/
23	(choriogonadotrop* or choriogonin or HCG or "h.c.g." or novarel or ovidrel or pregnyl or biogonadil or biogonadyl or chorulon or gonabion or "a.p.l." or apl or antuitrin-s or choragon or chorigon or chorex or choron or chorulon or coriantin or corion or endocorion or follutein or gestasol dry or gonacor or gonadex or gonadotropyl-c or gonatropin or homosten or ivf-c or libigen or ml-04a or ml04a or ovulgone or physex or praedyn or pranturon or predalon or pregnesin or primogonyl or profasi or promogonyl or prophasi or prymogonyl or pubergen or puberogen or riogon or synapoidin or zivafert).tw.
24	exp gonadorelin derivative/
25	((GnRH or GnRHa or gn-rh) adj4 (puls* or pump* or infus* or perfus* or intravenous* or subcutaneous* or stimulat* or therap* or treatment* or inject* or administ*)).tw.
26	(33515-09-2 or 51952-41-1 or 52699-48-6 or cystorelin or dirigestran or factrel or gonadoliberin or gonadorelin or kryptocur or luliberin).tw.
27	exp lifestyle/ or lifestyle modification/ or health promotion/
28	((lifestyle or life style) adj3 (change* or changing or adjust* or intervention* or modif* or restrict*)).tw.

#	Searches
29	(health* adj2 (life style or lifestyle or behavio?r* or promot*)).tw.
30	exercise/ or physical activity/ or kinesiotherapy/ or fitness/ or sport/
31	(exercise* or exercising or physical* activ* or fitness or train* or sport*).tw.
32	exp diet therapy/ or diet/ or healthy diet/
33	(diet* adj4 (therap* or modif* or restrict* or balance* or healthy or interven* or change* or changing or adjust* or behavio?r* or treatment*)).tw.
34	weight loss program/ or body weight loss/ or body weight gain/
35	((weight* or "body mass index" or "body mass indices" or "body fat index" or "body fat indexes" or "body fat indices" or BMI or BFI) adj1 (manage* or managing or regulat* or loss* or lose or reduc* or decreas* or gain* or increas* or optimiz* or optimis* or normalis* or normaliz*)).tw.
36	or/6-35
37	5 and 36
38	letter.pt. or letter/
39	note.pt.
40	editorial.pt.
41	case report/ or case study/
42	(letter or comment*).ti.
43	or/38-42
44	randomized controlled trial/ or random*.ti,ab.
45	43 not 44
46	animal/ not human/
47	nonhuman/
48	exp Animal Experiment/
49	exp Experimental Animal/
50	animal model/
51	exp Rodent/
52	(rat or rats or rodent* or mouse or mice).ti.
53	or/45-52
54	37 not 53
55	limit 54 to english language
56	limit 55 to dc=20110125-20230831
57	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
58	56 not 57
59	health economics/
60	exp economic evaluation/
61	exp health care cost/
62	exp fee/
63	budget/
64	funding/
65	resource allocation/
66	budget*.ti,ab.
67	cost*.ti,ab.
68	(economic* or pharmaco?economic*).ti,ab.
69	(price* or pricing*).ti,ab.
70	(financ* or fee or fees or expenditure* or saving*).ti,ab.
71	(value adj2 (money or monetary)).ti,ab.
72	resourc* allocat*.ti,ab.
73	(fund or funds or funding* or funded).ti,ab.
74	(ration or rations or rationing* or rationed).ti,ab.
75	or/59-74
76	quality adjusted life year/
77	"quality of life index"/
78	short form 12/ or short form 20/ or short form 36/ or short form 8/

#	Searches
79	sickness impact profile/
80	(quality adj2 (wellbeing or well being)).ti,ab.
81	sickness impact profile.ti,ab.
82	disability adjusted life.ti,ab.
83	(qal* or qtime* or qwb* or daly*).ti,ab.
84	(euroqol* or eq5d* or eq 5*).ti,ab.
85	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
86	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
87	(hui or hui1 or hui2 or hui3).ti,ab.
88	(health* year* equivalent* or hye or hyes).ti,ab.
89	discrete choice*.ti,ab.
90	rosser.ti,ab.
91	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
92	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
93	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
94	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
95	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
96	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
97	or/76-96
98	58 and (75 or 97)

Database: INAHTA

Date of last search: 03/08/2023

#	Searches
1	"Hypogonadism"[mh]
2	"Kallmann Syndrome"[mh]
3	(hypogonadotro* AND (hypogonadism or anovulation))
4	((gonadal or GnRH or "gonadotropin releasing hormone" or "gonadotrophin releasing hormone" or "gonadotropin-releasing hormone" or "gonadotrophin-releasing hormone") AND (failure* or inadequate* or abnormal* or deficien* or deficit* or defect*))
5	("secondary hypogonadism" or hypogonadotropism or hypogonadotrophism or "kallman syndrome" or "kallmans syndrome" or "kallmann syndrome" or "kallmanns syndrome")
6	#5 OR #4 OR #3 OR #2 OR #1

Database: HTA via CRD

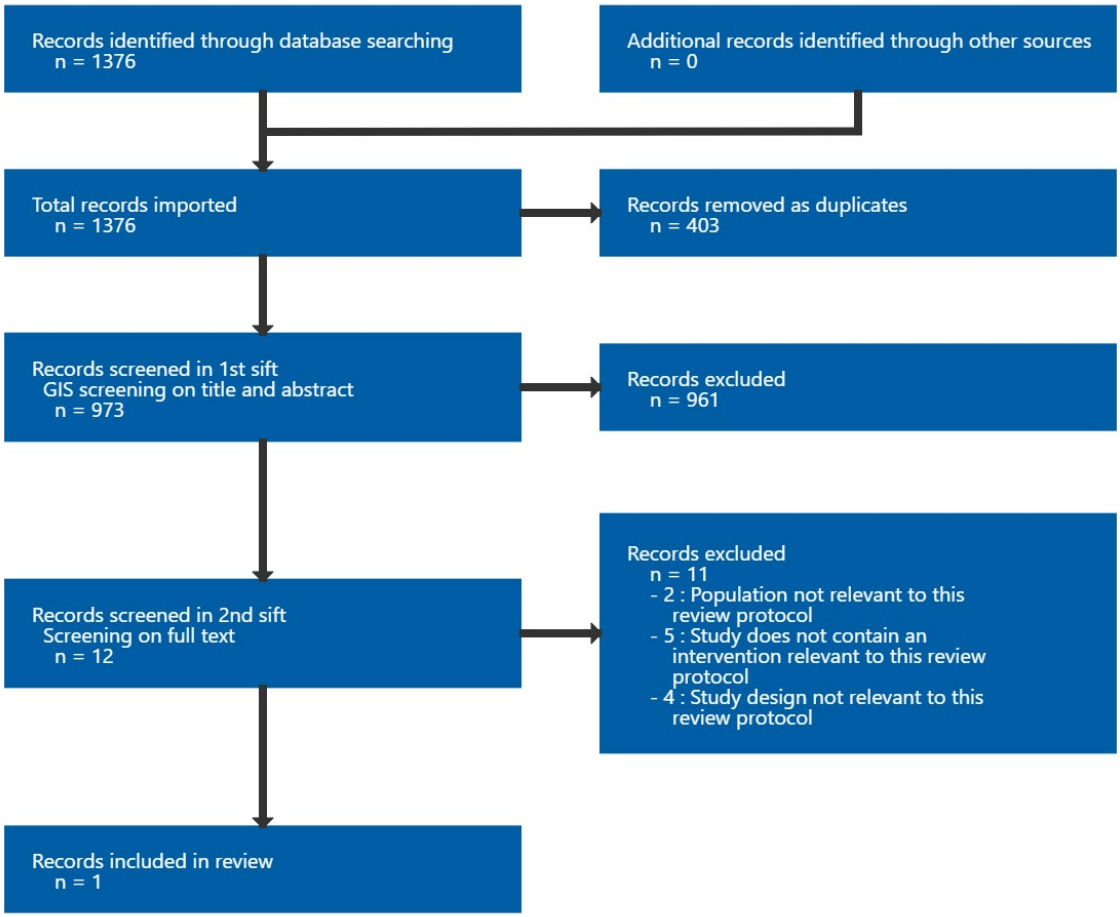
Date of last search: 03/08/2023

#	Searches
1	MeSH DESCRIPTOR Hypogonadism
2	MeSH DESCRIPTOR Kallmann Syndrome
3	(hypogonadotro* near4 (hypogonadism or anovulation))
4	((gonadal or GnRH or "gonadotropin releasing hormone" or "gonadotrophin releasing hormone") near4 (failure* or inadequate* or abnormal* or deficien* or deficit* or defect*))
5	("secondary hypogonadism" or hypogonadotropism or hypogonadotrophism or (kallman* next syndrome))
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#1 OR #2 OR #3 OR #4 OR #5) IN HTA

Appendix C Effectiveness evidence study selection

Study selection for: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Carone, 2012

Bibliographic Reference	Carone, D; Caropreso, C; Vitti, A; Chiappetta, R; Efficacy of different gonadotropin combinations to support ovulation induction in WHO type I anovulation infertility: clinical evidences of human recombinant FSH/human recombinant LH in a 2:1 ratio and highly purified human menopausal gonadotropin stimulation protocols.; Journal of endocrinological investigation; 2012; vol. 35 (no. 11); 996-1002

Study details

Country where study was carried out	Italy
Study type	Randomised controlled trial (RCT)
Study dates	July 2008 and November 2011
Inclusion criteria	All participants with: • WHO type I hypogonadotropic anovulation (diagnosed with hypogonadotropic hypogonadism according to a negative P4 challenge test) • serum LH<1.2 IU/l and FSH<5 IU/l • transvaginal ultrasound showing a uterus with a midline echo • no ovarian tumor or cyst and ≤13 small follicles (mean diameter ≤10mm) on the largest section through each ovary • a bone mineral index between 18.4 and 31.4

	• no systemic disease Most participants had primary amenorrhea (85.7%) while 5 participants (14.3%) had secondary amenorrhea
Exclusion criteria	Not reported
Patient characteristics	highly purified human menopausal gonadotropin (hMG-HP) human recombinant FSH (r-hFSH)/human recombinant LH (r-hLH) **Primary infertility: number (%)** hMG-HP: 16 (88) r-hFSH/r-hLH: 15 (88) **Age, years: Mean (SEM)** hMG-HP: 30.22 (3.64) r-hFSH/r-hLH: 30.58 (3.77) **BMI, kg/m2: Mean (SEM)** hMG-HP: 25.42 (3.35) r-hFSH/r-hLH: 23.48 (3.61) **P4, nmol/l: Mean (SEM)** hMG-HP: 0.48 (0.16) r-hFSH/r-hLH: 0.41 (0.19)

Intervention(s)/control	**highly purified human menopausal gonadotropin (hMG-HP)** 150 IU hMG-HP daily, as 150 IU FSH + 150 IU LH like activity **human recombinant FSH (r-hFSH)/human recombinant LH (r-hLH)** 150 IU r-hFSH and 75 IU r-hLH daily The FSH daily dose was fixed at 150 IU based upon clinical experience to ensure that all participants would be above their threshold needs. Both groups: participants received gonadotropin treatment for a maximum of 16 d and ovulation was induced by a single administration of hCG [10000 IU (IBSA)] on the day after the last hMG-HP or r-hFSH/r-hLH when the leading follicle had reached a mean diameter of ≥17 mm. Participants were initially treated for one cycle (series A) and, if consent was given, participants who did not become pregnant during the first cycle were treated for a further optional one cycle (series B) or two series (series C) of cycles, with the same criteria of randomization, that is maintaining the same treatment as the previous cycle.
Duration of follow-up	Follow-up at the end of each cycle (series A, series B, and series C)
Sources of funding	Sponsored by Centro Riproduzione e Andrologia
Sample size	**Total participant population**, N=35 participants hMG-HP: n=18 r-hFSH/r-hLH: n=17 **Series A participant population**, N=35 participants hMG-HP: n=18 r-hFSH/r-hLH: n=17

	Series B participant population, N=21 participants hMG-HP: n=14 r-hFSH/r-hLH: n=7 **Series C participant population,** N=14 participants hMG-HP: n=11 r-hFSH/r-hLH: n=3
Other information	Clinical trial registration number: NCT01623570

Study arms

hMG-HP (N = 18)

highly purified human menopausal gonadotropin (hMG-HP)

r-hFSH/r-hLH (N = 17)

human recombinant FSH (r-hFSH) plus human recombinant LH (r-hLH)

Outcomes

Outcome	**hMG-HP, N = 18**	**r-hFSH/r-hLH, N = 17**
Live birth (Series A) Defined in the study as live birth No of events	n = 4; % = 22	n = 9; % = 53

Outcome	hMG-HP, N = 18	r-hFSH/r-hLH, N = 17
Clinical pregnancy total/ participant Defined in the study as pregnancy No of events	n = 10; % = 55.56	n = 15; % = 88.23
Clinical pregnancy/cycle (Series A) No of events	n = 4; % = 22.22	n = 10; % = 58.82
Clinical pregnancy/cycle (Series B) No of events	n = 4; % = 28.57	n = 4; % = 57.14
Clinical pregnancy/cycle (Series C) No of events	n = 2; % = 18.18	n = 1; % = 33.33
Clinical pregnancy total/cycle (Series A, B and C) No of events	n = 10; % = 23.3	n = 15; % = 55.6
Miscarriage total/ participant Defined in the study as abortion No of events	n = 1; % = 5.55	n = 1; % = 5.88
Miscarriage/cycle (Series A) No of events	n = 0; % = 0	n = 1; % = 5.88
Miscarriage/cycle (Series B) No of events	n = 1; % = 7.14	n = 0; % = 0

Outcome	hMG-HP, N = 18	r-hFSH/r-hLH, N = 17
Miscarriage/cycle (Series C) No of events	n = 0; % = 0	n = 0; % = 0
Miscarriage total/cycle (Series A, B and C) No of events	n = 1; % = 2.32	n = 1; % = 3.7
Multiple gestation total/ participant Defined in the study as multiple pregnancy No of events	n = 3; % = 16.67	n = 2; % = 11.76
Multiple gestation/cycle (Series A) No of events	n = 1; % = 5.55	n = 2; % = 11.11
Multiple gestation/cycle (Series B) No of events	n = 1; % = 7.14	n = 0; % = 0
Multiple gestation/cycle (Series C) No of events	n = 1; % = 9.09	n = 0; % = 0
Multiple gestation total/cycle (Series A, B and C) No of events	n = 3; % = 6.98	n = 2; % = 7.41
Ovarian Hyperstimulation Syndrome Defined in the study as mild or moderate OHSS No of events	n = 0; % = 0	n = 0; % = 0

Live birth (Series A) - Polarity - Higher values are better

Clinical pregnancy (Series A, B and C) - Polarity - Higher values are better

Miscarriage (Series A, B and C) - Polarity - Lower values are better

Multiple gestation (Series A, B and C) - Polarity - Lower values are better

Ovarian Hyperstimulation Syndrome - Polarity - Lower values are better

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(There is no information about concealment of the allocation sequence, although baseline differences observed between intervention groups appear to be compatible with chance)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(It is likely that participants, carers, or people delivering the interventions were aware of intervention groups during the trial. No deviations from intended interventions arose because of the trial context however only participants who were unsuccessful in the first cycle and wished to continue with treatment were included in subsequent cycle analyses)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data were available for all, or nearly all, randomized participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(The method of measuring the outcome was not inappropriate and the measurement or ascertainment of the outcome did not differ between intervention groups. It is unlikely that the assessment of the outcome could not have been influenced by knowledge of the intervention received.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(The data were analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis and the result being assessed is unlikely to have been selected, based on the results, from multiple eligible outcome measurements within the outcome domain. The*

Section	Question	Answer
		reported outcome data are unlikely to have been selected, based on the results, from multiple eligible analyses of the data.)
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in two domains (Bias arising from the randomisation process and bias for deviations from the intended interventions, the effect of assignment to intervention) for this result, but not to be at high risk of bias for any domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RCT: randomised controlled trial; RoB: risk of bias

Appendix E Forest plots

Forest plots for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Table 5: Evidence profile for comparison between highly purified human menopausal gonadotropin (hMG-HP) and human recombinant follicle stimulating hormone/human recombinant luteinizing hormone (r-hFSH/r-hLH)

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hMG-HP	r-hFSH/ r-hLH	Relative (95% CI)	Absolute		
Live birth (defined in the study as live birth) per cycle - Series A; better indicated by higher values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/18 (22.2%)	9/17 (52.9%)	RR 0.42 (0.16 to 1.11)	307 fewer per 1000 (from 445 fewer to 58 more)	LOW	CRITICAL
Clinical pregnancy (defined in the study as pregnancy) all cycles (Series A, B and C) per participant; better indicated by higher values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/18 (55.6%)	15/17 (88.2%)	RR 0.63 (0.4 to 0.99)	326 fewer per 1000 (from 9 fewer to 529 fewer)	LOW	CRITICAL
Clinical pregnancy (defined in the study as pregnancy) all cycles (Series A, B and C) per cycle; better indicated by higher values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/43 cycles (23.3%)	15/27 cycles (55.6%)	RR 0.44 (0.23 to 0.86)	311 fewer per 1000 (from 78 fewer to 428 fewer)	LOW	CRITICAL
Clinical pregnancy (defined in the study as pregnancy) per cycle - Series A; better indicated by higher values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/18 (22.2%)	10/17 (58.8%)	RR 0.38 (0.15 to 0.98)	365 fewer per 1000 (from 12 fewer to 500 fewer)	LOW	CRITICAL
Clinical pregnancy (defined in the study as pregnancy) per cycle - Series B; better indicated by higher values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/14 (28.6%)	4/7 (57.1%)	RR 0.5 (0.18 to 1.43)	286 fewer per 1000 (from 469 fewer to 246 more)	VERY LOW	CRITICAL
Clinical pregnancy (defined in the study as pregnancy) per cycle - Series C; better indicated by higher values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/11 (18.2%)	1/3 (33.3%)	RR 0.55 (0.07 to 4.16)	150 fewer per 1000 (from 310 fewer to 1000 more)	VERY LOW	CRITICAL
Miscarriage (defined in the study as spontaneous abortion) all cycles (Series A, B and C) per participant; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/18 (5.6%)	1/17 (5.9%)	RR 0.94 (0.06 to 13.93)	4 fewer per 1000 (from 55 fewer to 761 more)	VERY LOW	IMPORTANT
Miscarriage (defined in the study as spontaneous abortion) all cycles (Series A, B and C) per cycle; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/43 cycles (2.3%)	1/27 cycles (3.7%)	RR 0.72 (0.08 to 6.49)	10 fewer per 1000 (from 34 fewer to 203 more)	VERY LOW	IMPORTANT
Miscarriage (defined in the study as spontaneous abortion) per cycle - Series A; better indicated by lower values												

1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/18 (0%)	1/17 (5.9%)	RR 0.32 (0.01 to 7.26)	40 fewer per 1000 (from 58 fewer to 368 more)	VERY LOW	IMPORTANT
Miscarriage (defined in the study as spontaneous abortion) per cycle - Series B; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/14 (7.1%)	0/7 (0%)	RR 1.6 (0.07 to 34.93)	Not applicable	VERY LOW	IMPORTANT
Miscarriage (defined in the study as spontaneous abortion) per cycle - Series C; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/11 (0%)	0/3 (0%)	not pooled	not pooled	VERY LOW	IMPORTANT
Multiple gestation (defined in the study as multiple pregnancy) all cycles (Series A, B and C) per participant; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/18 (16.7%)	2/17 (11.8%)	RR 1.42 (0.27 to 7.46)	49 more per 1000 (from 86 fewer to 760 more)	VERY LOW	IMPORTANT
Multiple gestation (defined in the study as multiple pregnancy) all cycles (Series A, B and C) per cycle; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/43 cycles (7%)	2/27 cycles (7.4%)	RR 0.8 (0.17 to 3.84)	15 fewer per 1000 (from 61 fewer to 210 more)	VERY LOW	IMPORTANT
Multiple gestation (defined in the study as multiple pregnancy) per cycle - Series A; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/18 (5.6%)	2/17 (11.8%)	RR 0.47 (0.05 to 4.74)	62 fewer per 1000 (from 112 fewer to 440 more)	VERY LOW	IMPORTANT
Multiple gestation (defined in the study as multiple pregnancy) per cycle - Series B; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/14 (7.1%)	0/7 (0%)	RR 1.6 (0.07 to 34.93)	Not applicable	VERY LOW	IMPORTANT
Multiple gestation (defined in the study as multiple pregnancy) per cycle - Series C; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/11 (9.1%)	0/3 (0%)	RR 1 (0.05 to 19.96)	Not applicable	VERY LOW	IMPORTANT
Ovarian Hyperstimulation Syndrome (OHSS: defined in the study as mild or moderate OHSS) all cycles (Series A, B and C) per participant; better indicated by lower values												
1 (Carone 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/18 (0%)	0/17 (0%)	Not applicable	RD 0.00 (-0.10, 0.10)	VERY LOW	IMPORTANT

CI: confidence interval; hMG-HP: highly purified human menopausal gonadotropin; MID: minimally important difference; OHSS: ovarian hyperstimulation syndrome; RD: risk difference; r-hFSH/r-hLH: human recombinant follicle stimulating hormone/human recombinant luteinizing hormone; RR: risk ratio

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] 95% CI crosses 1 MID for dichotomous outcomes (0.80 or 1.25)

[3] 95% CI crosses 2 MIDs for dichotomous outcomes (0.80 and 1.25)

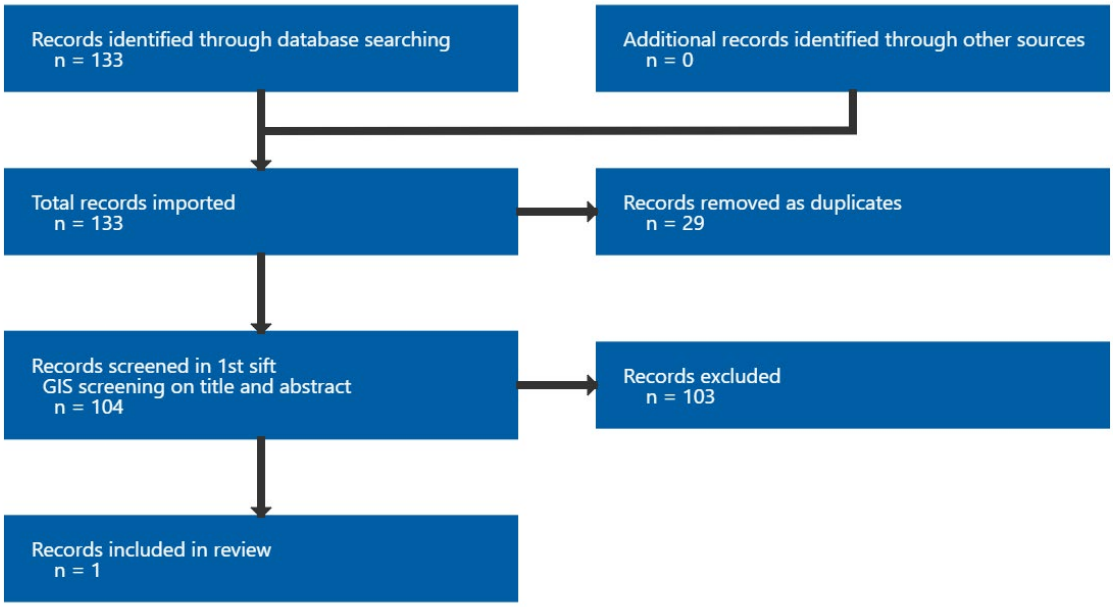
[4] N <150 events

Appendix G Economic evidence study selection

Study selection for: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Of 133 studies, 1 was assessed at full text level and included for this review.

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Table 6: Economic evidence tables

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Papaleo 2014 **Country:** Italy **Type of economic analysis:** CEA **Source of funding:** Merck Serono SpA	**Intervention in detail:** Recombinant gonadotropin therapy (rFSH + rLH) **Comparator in detail:** Urinary gonadotropin Therapy (HP-HMG)	**Population characteristics:** Hypogonadotropic hypogonadal women **Modelling approach:** Decision analytic Markov model **Source of baseline data:** Carone 2012 RCT **Source of effectiveness data:** Carone 2012 RCT **Source of cost data:** Carone 2012 RCT Expert opinion	Mean cost per participant: **Intervention:** €3,454 **Control:** €2,720 **Difference:** €734 **Mean outcome per participant:** **Clinical pregnancies**: **Intervention:** 0.87 **Control:**	**ICERs:** €2,007 per clinical pregnancy **Probability of being cost effective:** In 10,000 simulations recombinant therapy is more cost effective. It is also the most expensive treatment in the over-whelming majority of simulations. However, there is no cost-effectiveness threshold to determine the probability of being cost-effective. **Subgroup analysis:** N/A **Sensitivity analysis:** Only PSA undertaken.	**Currency:** Euro **Cost year:** 2013 **Time horizon:** Three treatment cycles **Discounting:** N/A **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:** Industry funded and parameters for probability distributions

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of unit cost data: Codifa database Italian regional outpatient examination pricelists	0.50 **Difference:** 0.33		used in a probabilistic sensitivity analysis were not specified.

CEA = Cost-effectiveness analysis, HP-HMG = highly purified human menopausal gonadotrophin; ICER = Incremental cost-effectiveness ratio; N/A = Not applicable; PSA = Probabilistic sensitivity analysis; RCT = Randomised control trial; rFSH = Human recombinant follicle stimulating hormone; rLH = recombinant luteinizing hormone

Appendix I Economic model

Economic model for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

Excluded effectiveness studies

Table 7: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Al-Inany, HG, Youssef, MA, Ayeleke, RO et al. (2016) Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database of Systematic Reviews	- Study does not contain an intervention relevant to this review protocol *Subfertile couples undergoing controlled ovarian hyperstimulation as part of an IVF or ICSI programme using GnRH antagonists or long-course GnRH agonist protocols for the prevention of premature LH surges*
Astrid EP, Cantineau, Mirjam J, Janssen, Ben J, Cohlen et al. (2014) Synchronised approach for intrauterine insemination in subfertile couples. Cochrane Database of Systematic Reviews 12(12): cd006942	- Population not relevant to this review protocol *The study does not appear to include people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism: subfertile couples where intrauterine insemination is the first treatment option such as unexplained subfertility, male subfertility, mild endometriosis, cervical hostility and cycle disturbances*
Bayram, N.; van Wely, M.; Van der Veen, F. (2003) Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database of Systematic Reviews 2010(11): cd000412	- Population not relevant to this review protocol *The study does not appear to include people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism: subfertile participants s with anovulation and polycystic ovary syndrome*
Chen, D, Shen, X, Fu, Y et al. (2020) Pregnancy Outcomes Following Letrozole Use in Frozen-thawed Embryo Transfer Cycles: A Systematic Review and Meta-analysis. Geburtshilfe und Frauenheilkunde 80(8): 820-833	- Study does not contain an intervention relevant to this review protocol *The study examines the clinical efficacy of letrozole for endometrial preparation prior to frozen-thawed embryo transfer*
D'Angelo, Arianna; Amso, Nazar N; Hassan, Rudaina (2017) Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. Cochrane Database of Systematic Reviews 5: cd002811	- Study does not contain an intervention relevant to this review protocol *The study examines withholding gonadotrophins (coasting) on the prevention of ovarian hyperstimulation syndrome in assisted reproduction cycles and trials that explored ovulation induction treatment without in vitro fertilisation or intra-cytoplasmic sperm injection were excluded*
Eftekhar, M. and Tabibnejad, N. (2021) Recombinant luteinizing hormone supplementation in assisted reproductive technology: a review of literature. Middle East Fertility Society Journal 26(1): 37	- Study design not relevant to this review protocol *The study is a literature review which narratively examines the effect of recombinant luteinizing hormone supplementation*
Ghobara, T; Gelbaya, TA; Ayeleke, RO (2017) Cycle regimens for frozen-thawed embryo	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
transfer. The Cochrane database of systematic reviews 7: cd003414	*The study examines the safety of natural cycle frozen-thawed embryo transfer (FET), hormone therapy cycle FET and ovulation induction cycle FET, and compares subtypes of these regimens*
Humaidan, P., Chin, W., Rogoff, D. et al. (2017) Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. Human Reproduction 32(3): 544-555	- Study does not contain an intervention relevant to this review protocol *Participants were women undergoing IVF and/or ICSI and were randomised to undergo controlled ovarian stimulation with r-hFSH/ r-hLH or r-hFSH*
Huseyin, Kiyak, Berk, Bulut, Tolga, Karacan et al. (2019) Management of ovulation induction and intrauterine insemination in infertile patients with hypogonadotropic hypogonadism. Journal of gynecology obstetrics and human reproduction 48(10): 833-838	- Study design not relevant to this review protocol *Non randomised study*
Ly, Nathalie; Dubreuil, Sophie; Touraine, Philippe (2022) Normal-high IGF-1 level improves pregnancy rate after ovarian stimulation in women treated with growth hormone replacement therapy. Endocrine connections 11(12)	- Study design not relevant to this review protocol *Non randomised study*
White, Davinia M, Hardy, Kate, Lovelock, Suzannah et al. (2018) Low-dose gonadotropin induction of ovulation in anovulatory women: still needed in the age of IVF. Reproduction (Cambridge, England) 156(1): f1-f10	- Study design not relevant to this review protocol *Non randomised study*

Excluded economic studies

No economic evidence was identified and then excluded for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of ovulation induction strategies for people with a health-related female factor fertility problem associated with hypogonadotropic hypogonadism?

No research recommendations were made for this review question.