National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

[B] Subclinical hypothyroidism

NICE guideline number NG257

Evidence reviews underpinning the research recommendation in the NICE guideline

March 2026

Final

Developed by NICE

Disclaimer

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

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

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Contents

Subclinical hypothyroidism

Review question

What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

Introduction

Clinical hypothyroidism, when people present with typical but non-specific symptoms such as tiredness, weight gain, feeling cold, muscle aches and weakness, dry and scaly skin, brittle hair and nails, is associated with subfertility. Treatment with levothyroxine until thyroid-stimulating hormone (TSH) levels fall within the normal reference range improves symptoms and prevents serious manifestations of thyroxine deficiency.

However, the effects of subclinical hypothyroidism (raised TSH levels but asymptomatic) on fertility are less clear.

The aim of this review is to determine if the treatment of subclinical hypothyroidism can improve female factor fertility problems.

Summary of the protocol

See Table 1 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 subclinical hypothyroidism (defined as an elevated TSH level ≥2.5 to <10 mIU/L and a normal serum free thyroxine concentration) as a known or suspected cause of their female factor health-related fertility problem. In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination.
Intervention	• Levothyroxine • Thyroxine
Comparison	• Placebo • No treatment
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) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as viable intrauterine pregnancy confirmed by ultrasound accounting for singleton pregnancy, twin pregnancy, and higher multiple pregnancy) **Important** • Miscarriage • Pregnancy loss (accounting for placental abruption) and stillbirth • Neonatal mortality • Gestational age at delivery

	• Birth weight • Major congenital anomaly

TSH: thyroid stimulating hormone

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 (supplement 1).

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

Effectiveness evidence

Included studies

A systematic review of the literature was conducted but no studies were identified which were applicable to this review question.

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

No studies were identified which were applicable to this review question (and so there are no evidence tables in Appendix D). No meta-analysis was conducted for this review (and so there are no forest plots in Appendix E).

Summary of the evidence

No studies were identified which were applicable to this review question (and so there are no GRADE tables in Appendix F).

Economic evidence

A total of 284 studies were identified in the health economic literature search for this review question. After duplicates were removed, 202 studies were screened on title and abstract of which all were excluded at this stage.

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Also see the literature search strategy in appendix B and the 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.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee agreed that live birth was a critical outcome because it is the most important outcome for people with fertility problems. The committee highlighted that it was also important to make clinical pregnancy a critical outcome. This reflects the evidence available, as pregnancy rates tend to be reported in preference to live birth rates. The committee were also aware that although pregnancy rates do not allow for differentiation between full-term pregnancy and pregnancy loss, clinical pregnancy is an indicator of improved fertility.

The committee agreed a number of other outcomes were important. For example, miscarriage and pregnancy loss were agreed to be important outcomes because they can be devastating for people trying to have a baby and can indicate when an intervention is effective for achieving pregnancy, but not for ensuring the safety of the baby to term. The committee agreed that neonatal mortality, gestational age at delivery, birth weight, and major congenital anomaly were important because they are measures of whether treating subclinical hypothyroidism is effective in ensuring the baby's health after they are born and can capture the potential harms of treatment with thyroid hormones.

The quality of the evidence

No studies were identified which were applicable to this review question.

Benefits and harms

One potentially relevant RCT was identified by the search (Abdel Rahman 2010) for this review. However, a Cochrane review (Akhtar 2019) on the topic excluded this study from their analysis due to concerns about the accuracy of the original data, and although a data correction had been issued, the results remained implausible. The committee also noted that the American Society for Reproductive Medicine (ASRM) had recently published a guideline on subclinical hypothyroidism in the infertile female population (ASRM 2024) and excluded this study, on the grounds that a relative risk ratio (RR) that is 4–8 times larger than the RRs in any other RCT is not plausible. The committee shared these concerns and agreed that this study could not be included in the review. No other eligible evidence was identified.

In the absence of any RCT evidence for levothyroxine treatment for subclinical hypothyroidism, and the potential costs of unnecessary screening, the committee agreed the routine measurement of thyroid function should not be offered to those without symptoms of thyroid disease.

The committee acknowledged that although there were no grounds to recommend routine screening or treatment of subclinical hypothyroidism due to the current lack of evidence, there remained uncertainty about potential benefits or harms associated with levothyroxine treatment. The committee therefore agreed to make a recommendation for further research (Appendix K) to address this gap.

Cost effectiveness and resource use

In the absence of any included evidence or original economic analysis, the committee made a qualitative assessment of the cost effectiveness of their recommendations.

The committee noted that subclinical hypothyroidism is inexpensive to treat but that the costs of screening to identify cases would also have to be taken into account. Therefore, the committee concluded, in the absence of any evidence of treatment benefit, that a cost-effective recommendation to treat subclinical hypothyroidism was not supported. As this leaves previous NICE guidance unchanged, no change to current practice or to NHS resource use is anticipated.

Recommendations supported by this evidence review

This evidence review supports the research recommendation on subclinical hypothyroidism.

References – included studies

Effectiveness

No studies were included in this review.

Other

Abdel Rahman 2010

Abdel Rahman, Ashraf Hany; Aly Abbassy, Hadeer; Abbassy, Aly Abd Elatif (2010) Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 16(5): 792-7

Akhtar 2019

Akhtar MA, Agrawal R, Brown J, Sajjad Y, Craciunas L. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD011009.

ASRM 2024

Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. Fertility and Sterility. 2024 May 1;121(5):765-82.

Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

Table 2: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023402100
1.	Review title	Clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems
2.	Review question	What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?
3.	Objective	To determine the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems. This will also inform decisions about whether people should be tested for subclinical hypothyroidism
4.	Searches	The following databases will be searched: Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Economic searches • MEDLINE ALL • Embase

ID	Field	Content
		• International Network of Agencies for Health Technology Assessment (INAHTA) • HTA Economic evaluations and quality of life filters will be applied. Searches will be restricted by: • English language • Human studies The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Treatments for subclinical hypothyroidism in females with fertility problems
6.	Population	Inclusion: • People with subclinical hypothyroidism (defined as TSH level ≥2.5<10 mIU/L and a normal serum free thyroxine [T4] concentration as well as an elevated serum TSH) as a known or suspected cause of their female factor health-related fertility problem. In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination.
7.	Intervention	• Levothyroxine • Thyroxine
8.	Comparator	• Placebo • No treatment
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual or cluster) If no RCT evidence:

ID	Field	Content
		• 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)
10.	Other exclusion criteria	Population: • People already being treated for known causes of subclinical hypothyroidism • People with clinical hypothyroidism defined as TSH level ≥10 mIU/L Other exclusion criteria: • Language limitations: studies published not in English-language • Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
11.	Context	This guidance will fully update 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) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as viable intrauterine pregnancy confirmed by ultrasound accounting for singleton pregnancy, twin pregnancy, and higher multiple pregnancy)
13.	Secondary outcomes (important outcomes)	• Miscarriage • Pregnancy loss (accounting for placental abruption) and stillbirth • Neonatal mortality • Gestational age at delivery • Birth weight • Major congenital anomaly
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 two reviewers, and consultation with senior staff if necessary.

ID	Field	Content
		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 if relevant, setting and follow-up, 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 possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixedeffects meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. 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. If heterogeneity cannot be explained through subgroup analyses then a random effects model will be used for meta-analysis, or the data will not be pooled. 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 • Validated scales/continuous outcomes: +/- 0.5x pooled control group SD for mean difference and SMD -0.5/0.5 for standardised mean difference • All other outcomes: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x pooled control group SD for mean difference and SMD -0.5/0.5 for standardised mean difference

ID	Field	Content	
17.	Analysis of sub-groups	Evidence will be stratified by: • Thresholds for defining subclinical hypothyroidism: ○ Subclinical hypothyroidism defined as TSH level between 2.5 mIU/L to 10.0 mIU/L ○ Subclinical hypothyroidism defined as TSH level between 4.0 mIU/L to 10.0 mIU/L • Antibody status ○ Thyroid antibody positive ○ Thyroid antibody negative Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • Age ○ <35 years ○ ≥35-39 years ○ ≥40-42 years ○ >42 years • Dose Where evidence is stratified or 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

ID	Field	Content		
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	February 2023		
22.	Anticipated completion date	November 2024		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
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		

ID	Field	Content	
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	
30.	URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=402100	
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, hypothyroidism, subclinical hypothyroidism	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published

ID	Field	Content	
		☐	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; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; SMD: standardised mean difference; TSH: thyroid-stimulating hormone

Appendix B Literature search strategies

Literature search strategies for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

Database: Ovid MEDLINE(R) ALL <1946 to July 26, 2024>

Date of last search: 29/07/2024

1	Fertility/ or Infertility/ or exp Infertility, Female/
2	(infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*).tw.
3	((inabilit* or unable or trying or try or fail* or difficult* or problem* or trouble* or issue*) adj4 conceiv*).tw.
4	(pre conception or preconception or conception).tw.
5	or/1-4
6	Pregnancy/ or pregnan*.tw.
7	Hypothyroidism/
8	((subclinical or "sub clinical" or mild* or borderline or early) adj2 (hypothyr* or hypo thyr* or hypo T)).tw.
9	(thyroid adj3 (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)).tw.
10	((thyroid stimulating hormone or TSH or thyr?otrop*) adj2 (elevat* or rais* or high* or level* or threshold* or concentration* or increas*)).tw.
11	(pre hypothyroidism* or prehypothyroidism).tw.
12	or/7-11
13	5 and 12
14	Thyroxine/
15	(berlthyrox or dexnon or eferox or eltroxin or eltroxine or euthyrox or eutirox or thyrox or thyroxin* or tetraiodothyronine or levo t or levothroid or levothyroid or levothyrox* or levoxine or levoxyl or lt4 or novothyral or novothyrox or oroxine or synthroid or synthrox or t4 or thyroid hormone or thevier or thyrax or tiroidine or tiroxina or unithroid or thyrox or althyxin or alverox or dicitirox or droxine or ermeza or eutroxsig or helmroxin or izifet or laevothyroxine or laevoxin or lethyrin or letrox or levaxin or leventa or levirox or levotiroxina or levotirsol or medithyrox or narval or pondtroxin or solsint or synotirex or syntroxine or teriston or thyquidity or thyradin or thyrex or thyrofix or thyrohelm or "thyro tabs" or "thyro 4" or thyrosit or tiche or tifactor or tirosint or tirosint or tirosintsol or tirosol or tiroxin or tsoludose or tyraq or vobenol or wolarex or thyronine or elthyrone or soloxine).tw.
16	or/14-15
17	6 and 12 and 16
18	13 or 17
19	letter/
20	editorial/
21	news/
22	exp historical article/
23	Anecdotes as Topic/
24	comment/
25	case reports/
26	(letter or comment*).ti.
27	or/19-26
28	randomized controlled trial/ or random*.ti,ab.
29	27 not 28
30	animals/ not humans/
31	exp Animals, Laboratory/
32	exp Animal Experimentation/
33	exp Models, Animal/
34	exp Rodentia/
35	(rat or rats or mouse or mice or rodent*).ti.

36	or/29-35
37	18 not 36
38	limit 37 to english language
39	randomized controlled trial.pt.
40	controlled clinical trial.pt.
41	pragmatic clinical trial.pt.
42	randomi#ed.ab.
43	placebo.ab.
44	randomly.ab.
45	Clinical Trials as topic.sh.
46	trial.ti.
47	or/39-46
48	Meta-Analysis/
49	Meta-Analysis as Topic/
50	(meta analy* or metanaly* or metaanaly*).ti,ab.
51	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
52	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54	(search* adj4 literature).ab.
55	(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.
56	cochrane.jw.
57	or/48-56
58	38 and (47 or 57)
59	Observational Studies as Topic/
60	Observational Study/
61	Epidemiologic Studies/
62	exp Case-Control Studies/
63	exp Cohort Studies/
64	Cross-Sectional Studies/
65	Controlled Before-After Studies/
66	Historically Controlled Study/
67	Interrupted Time Series Analysis/
68	Comparative Study.pt.
69	case control$.tw.
70	case series.tw.
71	(cohort adj (study or studies)).tw.
72	cohort analy$.tw.
73	(follow up adj (study or studies)).tw.
74	(observational adj (study or studies)).tw.
75	longitudinal.tw.
76	prospective.tw.
77	retrospective.tw.
78	cross sectional.tw.
79	or/59-78
80	38 and 79
81	80 not 58

Database: Embase <1974 to 2024 July 26>

Date of last search: 29/07/2024

1	fertility/ or infertility/ or female fertility/ or subfertility/ or female subfertility/
2	(infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*).tw.
3	((inabilit* or unable or trying or try or fail* or difficult* or problem*) adj4 conceiv*).tw.
4	(pre conception or preconception or conception).tw.
5	or/1-4
6	pregnancy/ or pregnan*.tw.
7	hypothyroidism/ or subclinical hypothyroidism/
8	((subclinical or "sub clinical" or mild* or borderline or early) adj2 (hypothyr* or hypo thyr* or hypo T)).tw.
9	(thyroid adj3 (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)).tw.
10	((thyroid stimulating hormone or TSH or thyr?otrop*) adj2 (elevat* or rais* or high* or level* or threshold* or concentration* or increas*)).tw.
11	(pre hypothyr* or prehypothyr*).tw.
12	or/7-11
13	5 and 12
14	thyroxine/ or levothyroxine/
15	(berlthyrox or dexnon or eferox or eltroxin or eltroxine or euthyrox or eutirox or thyrox or thyroxin* or tetraiodothyronine or levo t or levothroid or levothyroid or levothyrox* or levoxine or levoxyl or lt4 or novothyral or novothyrox or oroxine or synthroid or synthrox or t4 or thyroid hormone or thevier or thyrax or tiroidine or tiroxina or unithroid or thyrox or althyxin or alverox or dicitirox or droxine or ermeza or eutroxsig or helmroxin or izifet or laevothyroxine or laevoxin or lethyrin or letrox or levaxin or leventa or levirox or levotiroxina or levotirsol or medithyrox or narval or pondtroxin or solsint or synotirex or syntroxine or teriston or thyquidity or thyradin or thyrex or thyrofix or thyrohelm or "thyro tabs" or "thyro 4" or thyrosit or tiche or tifactor or tirosint or tirosint or tirosintsol or tirosol or tiroxin or tsoludose or tyraq or vobenol or wolarex or thyronine or elthyrone or soloxine).tw.
16	or/14-15
17	6 and 12 and 16
18	13 or 17
19	letter.pt. or letter/
20	note.pt.
21	editorial.pt.
22	case report/ or case study/
23	(letter or comment*).ti.
24	or/19-23
25	randomized controlled trial/ or random*.ti,ab.
26	24 not 25
27	animal/ not human/
28	nonhuman/
29	exp Animal Experiment/
30	exp Experimental Animal/
31	animal model/
32	exp Rodent/
33	(rat or rats or mouse or mice or rodent*).ti.
34	or/26-33
35	18 not 34
36	limit 35 to english language
37	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
38	36 not 37
39	random*.ti,ab.
40	factorial*.ti,ab.
41	(crossover* or cross over*).ti,ab.
42	((doubl* or singl*) adj blind*).ti,ab.

43	(assign* or allocat* or volunteer* or placebo*).ti,ab.
44	crossover procedure/
45	single blind procedure/
46	randomized controlled trial/
47	double blind procedure/
48	or/39-47
49	systematic review/
50	meta-analysis/
51	(meta analy* or metanaly* or metaanaly*).ti,ab.
52	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
53	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55	(search* adj4 literature).ab.
56	(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.
57	((pool* or combined) adj2 (data or trials or studies or results)).ab.
58	cochrane.jw.
59	or/49-58
60	38 and (48 or 59)
61	Clinical study/
62	Case control study/
63	Family study/
64	Longitudinal study/
65	Retrospective study/
66	comparative study/
67	Prospective study/
68	Randomized controlled trials/
69	67 not 68
70	Cohort analysis/
71	cohort analy$.tw.
72	(Cohort adj (study or studies)).tw.
73	(Case control$ adj (study or studies)).tw.
74	(follow up adj (study or studies)).tw.
75	(observational adj (study or studies)).tw.
76	(epidemiologic$ adj (study or studies)).tw.
77	(cross sectional adj (study or studies)).tw.
78	case series.tw.
79	prospective.tw.
80	retrospective.tw.
81	or/61-66,69-80
82	38 and 81
83	82 not 60

Database: Cochrane Database of Systematic Reviews Issue 7 of 12, July 2024

Date of last search: 29/07/2024

#1	MeSH descriptor: [Fertility] this term only
#2	MeSH descriptor: [Infertility] this term only
#3	MeSH descriptor: [Infertility, Female] explode all trees
#4	(infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*):ti,ab
#5	((inabilit* or unable or trying or try or fail* or difficult* or problem* or trouble* or issue*) near/4 conceiv*):ti,ab

#6	(pre next conception or preconception or conception):ti,ab
#7	{or #1-#6}
#8	MeSH descriptor: [Pregnancy] this term only
#9	pregnan*:ti,ab
#10	{or #8-#9}
#11	MeSH descriptor: [Hypothyroidism] this term only
#12	((subclinical or "sub clinical" or mild* or borderline or early) near/2 (hypothyr* or hypo next thyr* or hypo next T)):ti,ab
#13	(thyroid near/3 (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)):ti,ab
#14	(("thyroid stimulating hormone" or TSH or thyrotrophin* or thyrotropin* or thyrotropic or thyreotropin*) near/3 (elevat* or rais* or high* or level* or threshold* or concentration* or increas*)):ti,ab
#15	(pre next hypothyr* or prehypothyr*):ti,ab
#16	{or #11-#15}
#17	#7 and #16
#18	MeSH descriptor: [Thyroxine] this term only
#19	(berlthyrox or dexnon or eferox or eltroxin or eltroxine or euthyrox or eutirox or thyrox or thyroxin* or tetraiodothyronine or levo t or levothroid or levothyroid or levothyrox* or levoxine or levoxyl or lt4 or novothyral or novothyrox or oroxine or synthroid or synthrox or t4 or thyroid hormone or thevier or thyrax or tiroidine or tiroxina or unithroid or thyrox or althyxin or alverox or dicitirox or droxine or ermeza or eutroxsig or helmroxin or izifet or laevothyroxine or laevoxin or lethyrin or letrox or levaxin or leventa or levirox or levotiroxina or levotirsol or medithyrox or narval or pondtroxin or solsint or synotirex or syntroxine or teriston or thyquidity or thyradin or thyrex or thyrofix or thyrohelm or "thyro tabs" or "thyro 4" or thyrosit or tiche or tifactor or tirosint or tirosint or tirosintsol or tirosol or tiroxin or tsoludose or tyraq or vobenol or wolarex or thyronine or elthyrone or soloxine):ti,ab
#20	{or #18-#19}
#21	#10 and #16 and #20
#22	#17 or #21
#23	conference:pt or (clinicaltrials or trialsearch):so
#24	#22 not #23

Database: Cochrane Central Register of Controlled Trials Issue 7 of 12, July 2024

Date of last search: 29/07/2024

#1	MeSH descriptor: [Fertility] this term only
#2	MeSH descriptor: [Infertility] this term only
#3	MeSH descriptor: [Infertility, Female] explode all trees
#4	(infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*):ti,ab
#5	((inabilit* or unable or trying or try or fail* or difficult* or problem* or trouble* or issue*) near/4 conceiv*):ti,ab
#6	(pre next conception or preconception or conception):ti,ab
#7	{or #1-#6}
#8	MeSH descriptor: [Pregnancy] this term only
#9	pregnan*:ti,ab
#10	{or #8-#9}
#11	MeSH descriptor: [Hypothyroidism] this term only
#12	((subclinical or "sub clinical" or mild* or borderline or early) near/2 (hypothyr* or hypo next thyr* or hypo next T)):ti,ab
#13	(thyroid near/3 (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)):ti,ab
#14	(("thyroid stimulating hormone" or TSH or thyrotrophin* or thyrotropin* or thyrotropic or thyreotropin*) near/3 (elevat* or rais* or high* or level* or threshold* or concentration* or increas*)):ti,ab
#15	(pre next hypothyr* or prehypothyr*):ti,ab
#16	{or #11-#15}
#17	#7 and #16
#18	MeSH descriptor: [Thyroxine] this term only

#19	(berlthyrox or dexnon or eferox or eltroxin or eltroxine or euthyrox or eutirox or thyrox or thyroxin* or tetraiodothyronine or levo t or levothroid or levothyroid or levothyrox* or levoxine or levoxyl or lt4 or novothyral or novothyrox or oroxine or synthroid or synthrox or t4 or thyroid hormone or thevier or thyrax or tiroidine or tiroxina or unithroid or thyrox or althyxin or alverox or dicitirox or droxine or ermeza or eutroxsig or helmroxin or izifet or laevothyroxine or laevoxin or lethyrin or letrox or levaxin or leventa or levirox or levotiroxina or levotirsol or medithyrox or narval or pondtroxin or solsint or synotirex or syntroxine or teriston or thyquidity or thyradin or thyrex or thyrofix or thyrohelm or "thyro tabs" or "thyro 4" or thyrosit or tiche or tifactor or tirosint or tirosint or tirosintsol or tirosol or tiroxin or tsoludose or tyraq or vobenol or wolarex or thyronine or elthyrone or soloxine):ti,ab
#20	{or #18-#19}
#21	#10 and #16 and #20
#22	#17 or #21
#23	conference:pt or (clinicaltrials or trialsearch):so
#24	#22 not #23

Database: Epistemonikos

Date of last search: 29/07/2024

1	(title:((infertil* OR subfertil* OR fertil* OR steril* OR subfecund* OR fecund* OR infecund*)) OR abstract:((infertil* OR subfertil* OR fertil* OR steril* OR subfecund* OR fecund* OR infecund*))) OR (title:(((inabilit* OR unable OR trying OR try OR fail* OR difficult* OR problem* OR trouble* OR issue*) AND conceiv*)) OR abstract:(((inabilit* OR unable OR trying OR try OR fail* OR difficult* OR problem* OR trouble* OR issue*) AND conceiv*))) OR (title:(("pre conception" OR pre-conception OR preconception OR conception)) OR abstract:(("pre conception" OR pre-conception OR preconception OR conception)))
2	(title:(((subclinical OR "sub clinical" OR mild* OR borderline OR early) AND (hypothyr* OR hypo-thyr* OR hypo-T OR (hypo AND thyr*) OR "hypo T"))) OR abstract:(((subclinical OR "sub clinical" OR mild* OR borderline OR early) AND (hypothyr* OR hypo-thyr* OR hypo-T OR (hypo AND thyr*) OR "hypo T")))) OR (title:((thyroid AND (deficien* OR insufficien* OR underactive OR fail* OR low OR abnormal* OR decreas* OR lack* OR dysfunction* OR function* OR impair*))) OR abstract:((thyroid AND (deficien* OR insufficien* OR underactive OR fail* OR low OR abnormal* OR decreas* OR lack* OR dysfunction* OR function* OR impair*)))) OR (title:((("thyroid stimulating hormone" OR TSH OR thyr*) AND (elevat* OR rais* OR high* OR level* OR threshold* OR concentration* OR increas*))) OR abstract:((("thyroid stimulating hormone" OR TSH OR thyr*) AND (elevat* OR rais* OR high* OR level* OR threshold* OR concentration* OR increas*)))) OR (title:(((pre AND hypothyroidism*) OR pre-hypothyroidism* OR prehypothyroidism)) OR abstract:(((pre AND hypothyroidism*) OR pre-hypothyroidism* OR prehypothyroidism)))
3	1 AND 2 limited to SRs

Health Economic Literature search strategies

Database: Ovid MEDLINE(R) ALL <1946 to July 26, 2024>

Date of last search: 29/07/2024

1	Fertility/ or Infertility/ or exp Infertility, Female/
2	(infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*).tw.
3	((inabilit* or unable or trying or try or fail* or difficult* or problem* or trouble* or issue*) adj4 conceiv*).tw.
4	(pre conception or preconception or conception).tw.
5	or/1-4
6	Pregnancy/ or pregnan*.tw.
7	Hypothyroidism/
8	((subclinical or "sub clinical" or mild* or borderline or early) adj2 (hypothyr* or hypo thyr* or hypo T)).tw.
9	(thyroid adj3 (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)).tw.
10	((thyroid stimulating hormone or TSH or thyr?otrop*) adj2 (elevat* or rais* or high* or level* or threshold* or concentration* or increas*)).tw.
11	(pre hypothyroidism* or prehypothyroidism).tw.
12	or/7-11
13	5 and 12

14	Thyroxine/
15	(berlthyrox or dexnon or eferox or eltroxin or eltroxine or euthyrox or eutirox or thyrox or thyroxin* or tetraiodothyronine or levo t or levothroid or levothyroid or levothyrox* or levoxine or levoxyl or lt4 or novothyral or novothyrox or oroxine or synthroid or synthrox or t4 or thyroid hormone or thevier or thyrax or tiroidine or tiroxina or unithroid or thyrox or althyxin or alverox or dicitirox or droxine or ermeza or eutroxsig or helmroxin or izifet or laevothyroxine or laevoxin or lethyrin or letrox or levaxin or leventa or levirox or levotiroxina or levotirsol or medithyrox or narval or pondtroxin or solsint or synotirex or syntroxine or teriston or thyquidity or thyradin or thyrex or thyrofix or thyrohelm or "thyro tabs" or "thyro 4" or thyrosit or tiche or tifactor or tirosint or tirosint or tirosintsol or tirosol or tiroxin or tsoludose or tyraq or vobenol or wolarex or thyronine or elthyrone or soloxine).tw.
16	or/14-15
17	6 and 12 and 16
18	13 or 17
19	letter/
20	editorial/
21	news/
22	exp historical article/
23	Anecdotes as Topic/
24	comment/
25	case report/
26	(letter or comment*).ti.
27	or/19-26
28	randomized controlled trial/ or random*.ti,ab.
29	27 not 28
30	animals/ not humans/
31	exp Animals, Laboratory/
32	exp Animal Experimentation/
33	exp Models, Animal/
34	exp Rodentia/
35	(rat or rats or mouse or mice or rodent*).ti.
36	or/29-35
37	18 not 36
38	limit 37 to english language
39	quality-adjusted life years/
40	sickness impact profile/
41	(quality adj2 (wellbeing or well being)).ti,ab.
42	sickness impact profile.ti,ab.
43	disability adjusted life.ti,ab.
44	(qal* or qtime* or qwb* or daly*).ti,ab.
45	(euroqol* or eq5d* or eq 5*).ti,ab.
46	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48	(hui or hui1 or hui2 or hui3).ti,ab.
49	(health* year* equivalent* or hye or hyes).ti,ab.
50	discrete choice*.ti,ab.
51	rosser.ti,ab.
52	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58	or/39-57
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	38 and (58 or 79)

Database: Embase <1974 to 2024 July 26>

Date of last search: 29/07/2024

1	fertility/ or infertility/ or female fertility/ or subfertility/ or female subfertility/
2	(infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*).tw.
3	((inabilit* or unable or trying or try or fail* or difficult* or problem*) adj4 conceiv*).tw.
4	(pre conception or preconception or conception).tw.
5	or/1-4
6	pregnancy/ or pregnan*.tw.
7	hypothyroidism/ or subclinical hypothyroidism/
8	((subclinical or "sub clinical" or mild* or borderline or early) adj2 (hypothyr* or hypo thyr* or hypo T)).tw.
9	(thyroid adj3 (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)).tw.
10	((thyroid stimulating hormone or TSH or thyr?otrop*) adj2 (elevat* or rais* or high* or level* or threshold* or concentration* or increas*)).tw.
11	(pre hypothyr* or prehypothyr*).tw.
12	or/7-11
13	5 and 12
14	thyroxine/ or levothyroxine/
15	(berlthyrox or dexnon or eferox or eltroxin or eltroxine or euthyrox or eutirox or thyrox or thyroxin* or tetraiodothyronine or levo t or levothroid or levothyroid or levothyrox* or levoxine or levoxyl or lt4 or novothyral or novothyrox or oroxine or synthroid or synthrox or t4 or thyroid hormone or thevier or thyrax or tiroidine or tiroxina or unithroid or thyrox or althyxin or alverox or dicitirox or droxine or ermeza or eutroxsig or helmroxin or izifet or laevothyroxine or laevoxin or lethyrin or letrox or levaxin or leventa or levirox or levotiroxina or levotirsol or medithyrox or narval or pondtroxin or solsint or synotirex or syntroxine or teriston or thyquidity or thyradin or thyrex or thyrofix or thyrohelm or "thyro tabs" or "thyro 4" or thyrosit or tiche or tifactor or tirosint or tirosint or tirosintsol or tirosol or tiroxin or tsoludose or tyraq or vobenol or wolarex or thyronine or elthyrone or soloxine).tw.
16	or/14-15
17	6 and 12 and 16
18	13 or 17
19	letter.pt. or letter/
20	note.pt.

21	editorial.pt.
22	case report/ or case study/
23	(letter or comment*).ti.
24	or/19-23
25	randomized controlled trial/ or random*.ti,ab.
26	24 not 25
27	animal/ not human/
28	nonhuman/
29	exp Animal Experiment/
30	exp Experimental Animal/
31	animal model/
32	exp Rodent/
33	(rat or rats or mouse or mice or rodent*).ti.
34	or/26-33
35	18 not 34
36	limit 35 to english language
37	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
38	36 not 37
39	health economics/
40	exp economic evaluation/
41	exp health care cost/
42	exp fee/
43	budget/
44	funding/
45	resource allocation/
46	budget*.ti,ab.
47	cost*.ti,ab.
48	(economic* or pharmaco?economic*).ti,ab.
49	(price* or pricing*).ti,ab.
50	(financ* or fee or fees or expenditure* or saving*).ti,ab.
51	(value adj2 (money or monetary)).ti,ab.
52	resourc* allocat*.ti,ab.
53	(fund or funds or funding* or funded).ti,ab.
54	(ration or rations or rationing* or rationed).ti,ab.
55	or/39-54
56	quality adjusted life year/
57	"quality of life index"/
58	short form 12/ or short form 20/ or short form 36/ or short form 8/
59	sickness impact profile/
60	(quality adj2 (wellbeing or well being)).ti,ab.
61	sickness impact profile.ti,ab.
62	disability adjusted life.ti,ab.
63	(qal* or qtime* or qwb* or daly*).ti,ab.
64	(euroqol* or eq5d* or eq 5*).ti,ab.
65	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67	(hui or hui1 or hui2 or hui3).ti,ab.
68	(health* year* equivalent* or hye or hyes).ti,ab.
69	discrete choice*.ti,ab.
70	rosser.ti,ab.
71	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.

73	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77	or/56-76
78	38 and (55 or 77)

Database: INAHTA

Date of last search: 29/07/2024

15	#14 AND #9
14	#13 OR #12 OR #11 OR #10
13	(((hypothyr* or "hypo thyroidism" or "hypo T" or "pre hypothyroidism" or prehypothyr*))[Title] OR ((hypothyr* or "hypo thyroidism" or "hypo T" or "pre hypothyroidism" or prehypothyr*))[abs])
12	(("thyroid stimulating hormone" or TSH or thyrotrophin* or thyrotropin* or thyrotropic or thyreotropin*))[Title] OR (("thyroid stimulating hormone" or TSH or thyrotrophin* or thyrotropin* or thyrotropic or thyreotropin*))[abs]
11	((thyroid and (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)))[Title] OR ((thyroid and (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)))[abs]
10	Hypothyroidism[mh]
9	#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
8	(pregnan*)[Title] OR (pregnan*)[abs]
7	Pregnancy[mh]
6	(("pre conception" or preconception or conception))[Title] OR (("pre conception" or preconception or conception))[abs]
5	(((inabilit* or unable or trying or try or fail* or difficult* or problem* or trouble* or issue*) and conceiv*))[Title] OR (((inabilit* or unable or trying or try or fail* or difficult* or problem* or trouble* or issue*) and conceiv*))[abs]
4	((infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*))[Title] OR ((infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*))[abs]
3	Infertility, Female[mhe]
2	Infertility[mh]
1	Fertility[mh]

Database: HTA

Date of last search: 29/07/2024

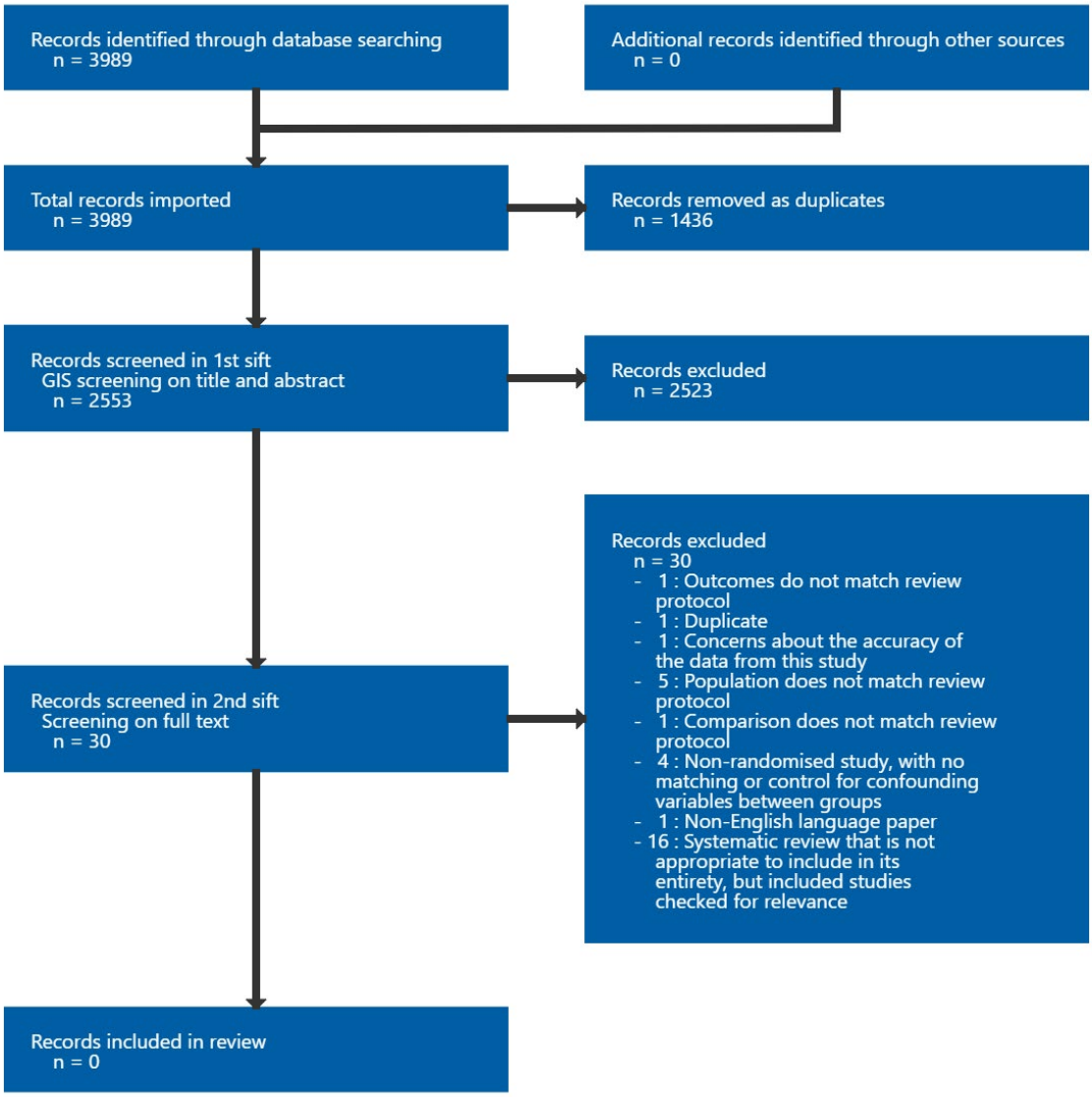
1	MeSH DESCRIPTOR fertility IN HTA
2	MeSH DESCRIPTOR Infertility IN HTA
3	MeSH DESCRIPTOR Infertility, Female EXPLODE ALL TREES IN HTA
4	((infertil* or subfertil* or fertil* or steril* or subfecund* or fecund* or infecund*))
5	(((inabilit* or unable or trying or try or fail* or difficult* or problem* or trouble* or issue*) adj4 conceiv*))
6	((pre conception or preconception or conception))
7	MeSH DESCRIPTOR Pregnancy IN HTA
8	(pregnan*)
9	MeSH DESCRIPTOR hypothyroidism IN HTA
10	((hypothyr* or "hypo thyroidism" or "hypo T" or "pre hypothyroidism" or prehypothyr*))
11	(("thyroid stimulating hormone" or TSH or thyrotrophin* or thyrotropin* or thyrotropic or thyreotropin*))
12	((thyroid and (deficien* or insufficien* or underactive or fail* or low or abnormal* or decreas* or lack* or dysfunction* or function* or impair*)))
13	#9 OR #10 OR #11 OR #12

14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
15	#13 AND #14
16	(*) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
17	#15 AND #16

Appendix C Effectiveness evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

No evidence was identified which was applicable to this review question.

Appendix E Forest plots

Forest plots for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

No evidence was identified which was applicable to this review question.

Appendix F GRADE tables

GRADE tables for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

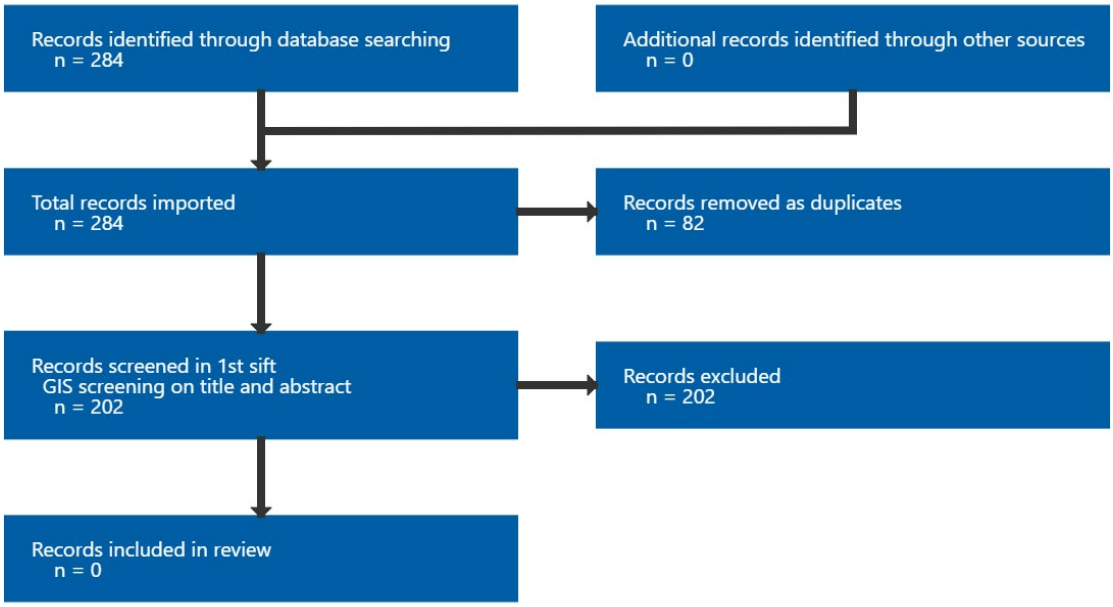
No evidence was identified which was applicable to this review question.

Appendix G Economic evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

No economic evidence was identified which was applicable to this review question.

Figure 2: Study selection flowchart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

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 treating subclinical hypothyroidism for female factor fertility problems?

Excluded effectiveness studies

Table 3: Excluded studies and reasons for their exclusion

Study	Reason
Abdel Rahman, Ashraf Hany; Aly Abbassy, Hadeer; Abbassy, Aly Abd Elatif (2010) Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 16(5): 792-7	- Concerns about the accuracy of the data from this study *A Cochrane review excluded this study from their analysis due to concerns about the accuracy of the original data, and although a data correction had been issued, the results remained implausible*
Akhtar, M Ahsan, Agrawal, Rina, Brown, Julie et al. (2019) Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. The Cochrane database of systematic reviews 6: cd011009	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance *Review has a wider scope than this review including people with euthyroid autoimmune thyroid disease, and therefore does not match this review's protocol*
Al-Anbari, L.A. (2017) Thyroxine supplementation improve intrauterine insemination outcome in patients with subclinical hypothyroidism. Journal of Pharmaceutical Sciences and Research 9(10): 1768-1772	- Non-randomised study, with no matching or control for confounding variables between groups
Bein, Magnus, Yu, Oriana Hoi Yun, Grandi, Sonia Marzia et al. (2021) Levothyroxine and the risk of adverse pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. BMC endocrine disorders 21(1): 34	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Busnelli, A, Beltratti, C, Cirillo, F et al. (2022) IMPACT OF THYROID AUTOIMMUNITY ON ASSISTED REPRODUCTIVE TECHNOLOGY OUTCOMES AND OVARIAN RESERVE MARKERS: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS. Thyroid : official journal of the American Thyroid Association 32(9): 1010-1028	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance

Study	Reason
Busnelli, Andrea; Cirillo, Federico; Levi-Setti, Paolo Emanuele (2021) Thyroid function modifications in women undergoing controlled ovarian hyperstimulation for in vitro fertilization: a systematic review and meta-analysis. Fertility and sterility 116(1): 218-231	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Busnelli, Andrea, Paffoni, Alessio, Fedele, Luigi et al. (2016) The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. Human reproduction update 22(6): 775-790	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Dhillon-Smith, Rima K, Middleton, Lee J, Sunner, Kirandeep K et al. (2019) Levothyroxine to increase live births in euthyroid women with thyroid antibodies trying to conceive: the TABLET RCT.	- Population does not match review protocol *Participants are euthyroid women (69% of population had TSH level<2.5mIU/L)*
Dhillon-Smith, Rima K, Middleton, Lee J, Sunner, Kirandeep K et al. (2019) Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. The New England journal of medicine 380(14): 1316-1325	- Duplicate
Galbiati, Francesca, Jokar, Tahereh Orouji, Howell, Lars M et al. (2024) Levothyroxine for a high-normal TSH in unexplained infertility. Clinical endocrinology 100(2): 192-198	- Non-randomised study, with no matching or control for confounding variables between groups
Janett-Pellegri, C, Moutzouri, E, Darbellay Farhoumand, P et al. (2020) [Treatment of subclinical hypothyroidism : an update of the evidence and the new Rapid Recommendations]. Revue medicale suisse 16(684): 455-458	- Non-English language paper
Johnson, N, Taylor-Christmas, A-K, Chatrani, V et al. (2015) Obstetric Outcomes of an Afro-Caribbean Cohort Following Universal Screening and Treatment of Subclinical Hypothyroidism. The West Indian medical journal 65(1): 78-82	- Non-randomised study, with no matching or control for confounding variables between groups
Kim, Chung-Hoon, Ahn, Jun-Woo, Kang, Sunjung Park et al. (2011) Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertility and sterility 95(5): 1650-4	- Comparison does not match review protocol *The control group in the study is not defined and it is unclear if the participants in this group received no treatment for hypothyroidism or placebo*

Study	Reason
Leng, Ting; Li, Xue; Zhang, Hong (2022) Levothyroxine treatment for subclinical hypothyroidism improves the rate of live births in pregnant women with recurrent pregnancy loss: a randomized clinical trial. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 38(6): 488-494	- Population does not match review protocol *Participants were pregnant women*
Meier, Christian, Christ-Crain, Mirjam, Guglielmetti, Merih et al. (2003) Prolactin dysregulation in women with subclinical hypothyroidism: effect of levothyroxine replacement therapy. Thyroid : official journal of the American Thyroid Association 13(10): 979-85	- Outcomes do not match review protocol *Study does not report any relevant outcomes: only thyroid hormone and PRL levels are reported*
Myneni, Revathi, Chawla, Harsh V, Grewal, Amit S et al. (2021) Thyroxine Replacement for Subfertile Females With Subclinical Hypothyroidism and Autoimmune Thyroiditis: A Systematic Review. Cureus 13(8): e16872	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Nazarpour, Sima, Ramezani Tehrani, Fahimeh, Amiri, Mina et al. (2019) Levothyroxine treatment and pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. Archives of gynecology and obstetrics 300(4): 805-819	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Negro, Roberto (2019) Levothyroxine before conception in women with thyroid antibodies: a step forward in the management of thyroid disease in pregnancy. Thyroid research 12: 5	- Non-randomised study, with no matching or control for confounding variables between groups *Commentary on Dhillon-Smith 2019*
Rao, Meng, Zeng, Zhengyan, Zhao, Shuhua et al. (2018) Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmuneity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. Reproductive biology and endocrinology : RB&E 16(1): 92	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Reid, Sally M, Middleton, Philippa, Cossich, Mary C et al. (2013) Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. The Cochrane database of systematic reviews: cd007752	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance

Study	Reason
Rotondi, Mario, Mazziotti, Gherardo, Sorvillo, Francesca et al. (2004) Effects of increased thyroxine dosage pre-conception on thyroid function during early pregnancy. European journal of endocrinology 151(6): 695-700	- Population does not match review protocol *Participants were women with primary (clinical) hypothyroidism*
Sankoda, Akiko, Suzuki, Hitomi, Imaizumi, Misa et al. (2024) Effects of Levothyroxine Treatment on Fertility and Pregnancy Outcomes in Subclinical Hypothyroidism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Thyroid : official journal of the American Thyroid Association 34(4): 519-530	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Sun, Xiaodong, Hou, Ningning, Wang, Hongsheng et al. (2020) A Meta-Analysis of Pregnancy Outcomes With Levothyroxine Treatment in Euthyroid Women With Thyroid Autoimmunity. The Journal of clinical endocrinology and metabolism 105(4)	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
van Dijk, Myrthe M, Vissenberg, Rosa, Fliers, Eric et al. (2022) Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The lancet. Diabetes & endocrinology 10(5): 322-329	- Population does not match review protocol *Participants are euthyroid women with thyroid peroxidase antibodies and a history of ≥2 miscarriages. Included participants had TSH levels of 1.36-3.11 mIU/L but the study does not report how many participants had ≥2.5 mIU/L and their results are not reported separately. Participants' average TSH level is 2.05 mIU/L*
Velkeniers, B, Van Meerhaeghe, A, Poppe, K et al. (2013) Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. Human reproduction update 19(3): 251-8	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Vissenberg, R., Van Den Boogaard, E., Van Der Post, J.A. et al. (2011) Treatment of (sub) clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: A systematic review. Journal of Reproductive Immunology: 148-149	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Vissenberg, R., Van Den Boogaard, E., Van Wely, M. et al. (2012) Treatment of (sub) clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: A systematic review. Human Reproduction	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance

Study	Reason
Vissenberg, R, van den Boogaard, E, van Wely, M et al. (2012) Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. Human reproduction update 18(4): 360-73	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance
Wang, Haining, Gao, Hongwei, Chi, Hongbin et al. (2017) Effect of Levothyroxine on Miscarriage Among Women With Normal Thyroid Function and Thyroid Autoimmunity Undergoing In Vitro Fertilization and Embryo Transfer: A Randomized Clinical Trial. JAMA 318(22): 2190-2198	- Population does not match review protocol *Participants were euthyroid women (median TSH levels 2.94mIU/L and 2.12mIU/L for the intervention and control groups, respectively)*
Wang, X, Zhang, Y, Tan, H et al. (2020) Effect of levothyroxine on pregnancy outcomes in women with thyroid autoimmunity: a systematic review with meta-analysis of randomized controlled trials. Fertility and sterility 114(6): 1306-1314	- Systematic review that is not appropriate to include in its entirety, but included studies checked for relevance

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of treating subclinical hypothyroidism for female factor fertility problems?

K.1.1 Research recommendation

What are the benefits and harms of levothyroxine for the treatment of subclinical hypothyroidism in women, trans men and non-binary people who are receiving fertility treatment?

K.1.2 Why this is important

Clinical (or overt) hypothyroidism is associated with subfertility. However, the impact of subclinical hypothyroidism (raised TSH levels but asymptomatic) on fertility is less clear. Evidence from some cohort studies suggest there may be adverse effects (including miscarriage, preterm birth, and obstetric complications) associated with untreated subclinical hypothyroidism. However, without a robust evidence base, the potential benefit of treating subclinical hypothyroidism remains unclear.

K.1.3 Rationale for research recommendation

Table 4: Research recommendation rationale

Importance to 'patients' or the population	Little is known about potential benefits or harms of levothyroxine treatment for subclinical hypothyroidism in women, trans men and non-binary people who are receiving fertility treatment. If important benefits were shown for this relatively inexpensive and non-invasive treatment, this would be an important treatment option for patients to consider
Relevance to NICE guidance	The previous version of the NICE guideline recommended that estimation of thyroid function should be confined to those with symptoms of thyroid disease, based on evidence that females with possible fertility problems are no more likely than the general population to have thyroid disease. However, if levothyroxine treatment was shown to be clinically and cost effective, routine screening of thyroid function would need to be extended
Relevance to the NHS	The outcome would affect the treatment options available for fertility problems provided by the NHS
National priorities	Reduction in risk of miscarriage and improved outcomes for neonates
Current evidence base	No randomised clinical trial evidence for levothyroxine treatment (prior to pregnancy) in females with subclinical hypothyroidism and fertility problems
Equality considerations	None known

K.1.4 Modified PICO table

Table 5: Research recommendation modified PICO table

Population	People with subclinical hypothyroidism (defined as TSH level ≥2.5<10 mIU/L and a normal serum free thyroxine [T4] concentration as well

	as an elevated serum TSH) and subfertility (defined as pregnancy not achieved after 12 months of regular unprotected sexual intercourse or after 6 cycles of artificial insemination)
Intervention	Levothyroxine
Comparator	Placebo
Outcome	• Live birth • Clinical pregnancy • Miscarriage • Pregnancy loss (accounting for placental abruption) and stillbirth • Neonatal mortality • Gestational age at delivery • Birth weight
Study design	RCT
Timeframe	Follow-up to pregnancy loss or live birth
Additional information	None

RCT: randomised controlled trial; TSH: thyroid-stimulating hormone