National Institute for Health and Care Excellence

Draft for consultation

Fertility problems: assessment and treatment

[D] Endometrial receptivity testing

NICE guideline number NGXXX

Evidence review underpinning recommendation 1.10.5 and research recommendation in the NICE guideline

September 2025

Draft for consultation

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Endometrial receptivity testing

Review question

What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Introduction

The uterus is only receptive to the implantation of an embryo at a specific time, which usually occurs 7 to 9 days after ovulation (known as the 'window of implantation'), and the endometrial receptivity is influenced by the sequential effects of oestrogen and progesterone. An endometrial biopsy can determine endometrial gene expression, and this can be used to determine if the endometrium is pre-receptive, early receptive, receptive, late receptive or post receptive. In addition, tests of the endometrial biome can be used to determine the proportions of healthy endometrial bacteria and bacteria that can cause endometritis, and so determine whether the endometrium is likely to be receptive to implantation. Ideally replacement of embryos after IVF would take place when the endometrium is in a receptive state, and therefore it has been proposed that tests of endometrial receptivity can be used to optimise outcomes from IVF.

The aim of this review is to determine if tests for endometrial receptivity are effective at improving outcomes for IVF when added to the standard IVF procedures.

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 undergoing tests for endometrial receptivity as an add-on to treatment for a 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	Embryo transfer following tests for endometrial receptivity, including: • Gene expression analysis such as Endometrial Receptivity Array (ERA) • Microbiological analysis such as Endometria Microbiome Metagenomic Analysis (EMMA) or Analysis of Infectious Chronic Endometritis (ALICE)
Comparison	Standard embryo transfer without test for endometrial receptivity
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 an ultrasound scan that has shown at least one fetal heart rate) **Important** • Miscarriage • Ectopic pregnancy

	• Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Multiple gestation

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

Two randomised controlled trials (RCTs) were included for this review (Doyle 2022 and Simon 2020).

The included studies are summarised in Table 2.

Both studies compared endometrial receptivity test-timed frozen embryo transfer using the Endometrial Receptivity Array (ERA) with standard frozen embryo transfer (Doyle 2022 and Simon 2020), and 1 of these studies additionally compared endometrial receptivity test-timed frozen embryo transfer (using ERA) with standard fresh embryo transfer (Simon 2020).

Both studies included participants with a mean age <35 years. Both studies excluded participants with recurrent implantation failure, defined either as >2 embryo transfers not resulting in ongoing pregnancy since the participant's last live birth, if any (Doyle 2022), or as >3 failed IVF cycles with good quality embryos transferred (Simon 2020). Both studies included participants with and without previous failed embryo transfer or IVF, with 12-15% of participants in each study having previous embryo transfer/IVF failure (Doyle 2022 and Simon 2020, respectively).

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

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Doyle 2022 RCT US	N=767 people undergoing frozen embryo transfer Receptivity-timed frozen embryo transfer group (n=381):	Receptivity-timed frozen embryo transfer Single euploid frozen embryo transfer as recommended by	Standard frozen embryo transfer Single euploid frozen embryo transfer 123 ± 3 hours after initiation of	• Live birth • Clinical pregnancy • Miscarriage: ○ Total pregnancy loss ○ Clinical pregnancy loss	Participants in both groups received the following: • Exogenous estradiol, plus once endometrial

Study	Population	Intervention	Comparison	Outcomes	Comments
	• Mean age (SD): 34.7 (2.7) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • History of failed embryo transfer/s: 32 (9%) • History of live birth/s: 67 (18%) Standard frozen embryo transfer group (n=386): • Mean age (SD): 34.5 (2.7) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • History of failed embryo transfer/s: 26 (7%) • History of live birth/s: 66 (17%)	endometrial receptivity results (using ERA): • If the result was receptive, transfer was performed at standard timing • If the result was nonreceptive, relative to standard timing, transfer was performed: ○ 12 hours earlier if result was late receptive ○ 12 hours later if the result was early receptive ○ 24 hours earlier if the result was post-receptive ○ 24 or more hours later if the result was pre-receptive (the specific recommended adjustment ranged from 24-48 hours later for pre-receptive results)	progesterone (standard timing)	○ Biochemical pregnancy loss • Ectopic pregnancy • Pregnancy loss (biochemical or clinical pregnancy loss; ectopic pregnancy; stillbirth; therapeutic abortion)	thickness reached ≥7 mm with serum progesterone <1.5 ng/mL, either 50 mg of intramuscular progesterone daily or 50 mg of intramuscular progesterone every third day, plus 200 mg twice daily of Endometrin • Endometrial pipelle biopsy for endometrial receptivity testing 123 ± 3 hours after the first progesterone injection, plus repeat testing if endometrial receptivity results were non-informative • The same luteal support regimen as during their endometrial receptivity cycle • Continuation of exogenous estradiol and progesterone for participants with appropriate pregnancy development until 10 weeks' estimated gestational age.
Simon 2020	N=458 infertile women undergoing IVF Personalised embryo transfer group (n=148): • Mean age (SD):	<u>Personalised embryo transfer</u> • The endometrium was prepared for the cycle to carry out the ERA test and 1 or 2 endometrial	<u>Frozen embryo transfer</u> • Properly developed blastocysts were vitrified using different protocols	• Live birth • Clinical pregnancy • Miscarriage: ○ Total pregnancy loss ○ Clinical pregnancy loss	Participants in all groups received the following: • Ovarian stimulation using standard protocols in each of the participant

Study	Population	Intervention	Comparison	Outcomes	Comments
	33 (3.1) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • Previous IVF failure: ○ No previous failed IVF: 109 (74%) ○ 1 previous failed IVF: 20 (14%) ○ 2 previous failed IVF: 10 (7%) ○ 3 previous failed IVF: 6 (4%) ○ Unknown: 3 (2%) • History of live birth/s: ○ 1 previous delivery: 11 (7%) ○ ≥2 previous deliveries: 3 (2%) • Transfers: ○ Mean embryos per transfer (SD): 1.52 (0.5) ○ Cumulative number of transfers*: 282 Frozen embryo transfer group (n=154): • Mean age (SD): 32.8 (3.4) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • Previous IVF failure:	biopsies (the timing of the second biopsy depended on the result of the first) were collected from the uterine fundus using a Pipelle catheter from or similar, then the endometrial tissue was shipped for ERA test • Properly developed blastocysts were vitrified using different protocols depending on the IVF laboratory • Embryo transfer was carried out in an HRT cycle at the timing indicated by the ERA test	depending on the IVF laboratory • Frozen embryo transfer was carried out in an HRT cycle. Further information about the timing is not reported • Patients received transfer during a hormonal replacement therapy cycle after embryo thawing, following the protocol and timing used in each clinic <u>Fresh embryo transfer</u> • Embryo transfer was carried out 5 or 6 days after oocyte retrieval according to blastocyst timing • Luteal phase supplementation route and dosage were determined by the participant physician or clinic	○ Biochemical pregnancy • Ectopic pregnancy • Pregnancy loss (total pregnancy loss; ectopic pregnancy; elective termination of pregnancy • Multiple gestation	sites according to female age, basal hormone levels, basal ovarian reserve and BMI • ICSI or IVF according to the protocols of the participating sites

Study	Population	Intervention	Comparison	Outcomes	Comments
	○ No previous failed IVF: 104 (68%) ○ 1 previous failed IVF: 23 (15%) ○ 2 previous failed IVF: 10 (7%) ○ 3 previous failed IVF: 11 (7%) ○ Unknown: 6 (4%) • History of live birth/s: ○ 1 previous delivery: 16 (10%) ○ ≥2 previous deliveries: 4 (3%) • Transfers: ○ Mean embryos per transfer (SD): 1.61 (0.5) ○ Cumulative number of transfers*: 267 Fresh embryo transfer group (n=156): • Mean age (SD): 32.7 (3.3) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • Previous IVF failure: ○ No previous failed IVF: 112 (72%) ○ 1 previous failed IVF: 22 (14%) ○ 2 previous failed IVF: 12 (8%) ○ 3 previous				

Study	Population	Intervention	Comparison	Outcomes	Comments
	failed IVF: 6 (4%) ○ Unknown: 4 (3%) • History of live birth/s: ○ 1 previous delivery: 17 (11%) ○ ≥2 previous deliveries: 3 (2%) • Transfers: ○ Mean embryos per transfer (SD): 1.63 (0.5) ○ Cumulative number of transfers*: 248 *Cumulative number of transfers includes all embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period				

ERA: Endometrial Receptivity Array; HRT: hormone replacement therapy; ICSI: intracytoplasmic sperm injection; IVF: in-vitro fertilisation; N: number; RCT: randomised controlled trial; SD: standard deviation

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

There was no important difference found between frozen embryo transfer guided by the ERA and standard frozen embryo transfer for the outcomes live birth, clinical pregnancy, miscarriage (total, clinical, or biochemical pregnancy loss), ectopic pregnancy, pregnancy loss, multiple gestation, or any of the cumulative versions of these outcomes. This evidence ranged from high to very low quality, with the outcome live birth being of high quality, and clinical pregnancy and pregnancy loss being of moderate quality.

There was no important difference found between frozen embryo transfer guided by the ERA and standard fresh embryo transfer for the outcomes live birth, cumulative live birth, clinical pregnancy, cumulative clinical pregnancy, miscarriage (total pregnancy loss, cumulative total pregnancy loss, biochemical pregnancy loss, or cumulative biochemical pregnancy loss), ectopic pregnancy, cumulative ectopic pregnancy, pregnancy loss, or cumulative pregnancy loss. The risk of miscarriage (clinical pregnancy loss and cumulative clinical pregnancy loss) was lower in the standard fresh embryo transfer group. The risk of multiple live birth and cumulative multiple live birth was lower in the frozen embryo transfer guided by the ERA group. This evidence all ranged from low to very low quality, with only miscarriage being of low quality.

There was no evidence on the effectiveness of microbiological analysis tests such as EMMA (Endometria Microbiome Metagenomic Analysis) or ALICE (Analysis of Infectious Chronic Endometritis).

See appendix F for full GRADE tables.

Economic evidence

A total of 496 studies were identified in the health economic search for this review question. After duplicates were removed, 320 studies were sifted 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.

Unit costs

Table 3: Unit costs

Resource	Unit costs	Source
Endometrial receptivity testing	£795	Liverpool Women's NHS foundation trust[(a)]

(a) Cost obtained from an Information leaflet. The leaflet states that endometrial receptivity testing is offered at a non-profit price and therefore this cost should be largely reflective of the cost for endometrial receptivity testing in the UK

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 agreed that it was also important to make clinical pregnancy a critical outcome as this reflects the evidence available because clinical pregnancy rates tend to be reported in preference to live birth rates throughout the literature. 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, pregnancy loss, and ectopic pregnancy were agreed to be important outcomes because they can be devastating for people trying to have a baby and may indicate that although a pregnancy has been achieved it does not lead to a live birth. The committee

agreed that multiple gestation was important because it creates a greater risk for complications in pregnancy and during delivery, such as early birth.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology and was rated as moderate to very low quality. When evidence was downgraded, this was mainly because of risk of bias assessed using version 2 of the Cochrane RoB tool, imprecision in the effect estimate, publication bias in the case of 1 study (Simon 2020), and, for 1 outcome, serious heterogeneity unexplained by subgroup analysis. When outcomes were downgraded for risk of bias, this was because of deviations from the intended interventions and selection of the reported result.

There was no evidence on the effectiveness of microbiological analysis tests such as EMMA (Endometria Microbiome Metagenomic Analysis) or ALICE (Analysis of Infectious Chronic Endometritis).

Benefits and harms

The committee agreed that moderate quality evidence showed no important difference between ERA-timed frozen embryo transfer and standard frozen embryo transfer for the critical outcomes of live birth and clinical pregnancy. Similarly, there was very low quality evidence showing no difference in both these critical outcomes for the comparison of ERA-timed frozen embryo transfer and standard fresh embryo transfer.

Although there was some evidence that ERA-timed frozen embryo transfer had a lower risk of multiple gestation compared to fresh embryo transfer, this evidence was very low quality and the committee agreed that this outcome alone did not justify the risks associated with performing an endometrial biopsy (such as cramping, bleeding, infection, and uterine perforation), when there was no additional benefit for live birth or clinical pregnancy. Additionally, there was low quality evidence that standard fresh embryo transfer had a lower risk of clinical pregnancy loss compared to ERA-timed frozen embryo transfer.

The committee highlighted that the participants in the primary studies may differ in important ways from people that the test would be offered to in clinical practice. For instance, the studies excluded people with recurrent implantation failure and included only those with euploid blastocysts available for embryo transfer, which is likely to have an important impact on the success of implantation. However, the committee reflected that these more restrictive exclusion and inclusion criteria made it easier to evaluate the effectiveness of ERA as most embryonic issues have been controlled for, and therefore confirmed that if ERA was not effective at increasing fertility outcomes in these situations it was not likely to be effective in a ’real world’ situation.

Based on the available evidence showing no important benefits of ERA the committee agreed that genetic expression analysis (including ERA) should not be offered as a treatment add-on to people with fertility problems.

The committee discussed the absence of eligible evidence on microbiological analysis such as Endometria Microbiome Metagenomic Analysis (EMMA) or Analysis of Infectious Chronic Endometritis (ALICE). While gene expression analysis (such as ERA) is used to identify the optimal time window for embryo transfer, EMMA and ALICE are used to identify endometrial bacteria and to determine whether the endometrium is likely to be receptive to implantation. The committee highlighted that abnormal results of microbiological or microbiome tests for endometrial receptivity would inform treatment such as antibiotics or microbiota transplantation, and evidence on the effectiveness of such treatment would be needed in order to recommend microbiological analysis as a treatment add-on to people with fertility problems. As there was a lack of evidence for a test-and-treat strategy using

microbiome/microbiological tests to optimise IVF outcomes the committee made a research recommendation. See appendix K for further details.

Cost effectiveness and resource use

In the absence of any included health economic evidence, or original economic modelling, the committee made a qualitative assessment of the cost-effectiveness for endometrial receptivity testing.

The committee discussed that, in general, fertility add-ons increase the cost of each round of IVF. A cost estimate of £795 was obtained for endometrial receptivity testing and therefore, given the clinical evidence indicated no important differences, the committee concluded that additional costs associated with endometrial receptivity testing would not represent a cost-effective use of NHS resources. The committee therefore made a do not offer recommendation.

As endometrial receptivity testing is not currently provided in current NHS practice, there will be no resource impact associated with this recommendation.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.10.5 and the research recommendation on endometrial receptivity testing.

References – included studies

Effectiveness

Doyle 2022

Doyle, Nicole, Jahandideh, Samad, Hill, Micah J et al. (2022) Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization: A Randomized Clinical Trial. JAMA 328(21): 2117-2125

Simon 2020

Simon, Carlos, Gomez, Carlos, Cabanillas, Sergio et al. (2020) A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. Reproductive biomedicine online 41(3): 402-415

Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023410108
1.	Review title	Clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment
2.	Review question	What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?
3.	Objective	To determine the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment
4.	Searches	The following databases will be searched (from 2000 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 full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Fertility treatment add-ons
6.	Population	Inclusion: • People undergoing tests for endometrial receptivity as an add-on to treatment for a 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.	Interventions	Tests for endometrial receptivity, including: • Gene expression analysis (for example, ERA [Endometrial Receptivity Array]) • Microbiological analysis (for example, EMMA [Endometria Microbiome Metagenomic Analysis]; ALICE [Analysis of Infectious Chronic Endometritis])
8.	Comparators	Standard embryo transfer without test for endometrial receptivity
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs • If no RCTs: ○ Quasi-randomised controlled trials (experimental studies using a non-randomly assigned control group design with match comparison or another method of controlling for confounding variables)
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)

ID	Field	Content
		• 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 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 an ultrasound scan that has shown at least one fetal heart rate)
13.	Secondary outcomes (important outcomes)	• Miscarriage • Ectopic pregnancy • Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Multiple gestation
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. 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, participant characteristics, inclusion and exclusion criteria, details of the interventions, 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 for RCTs (and quasi-RCTs, if no RCT evidence identified) 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

ID	Field	Content
		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, 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 • All other outcomes: 0.8 and 1.25 for all relative dichotomous outcomes

17.	Analysis of sub-groups	Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:
		• Age (based on the mean age in the study):
		  ○ <35 years
		  ○ ≥35 years
		• Previous implantation failure
		  ○ First embryo transfer
		  ○ After previous failed embryo transfer
		
		Where evidence is sub grouped 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.

ID	Field	Content			
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	March 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**			

ID	Field	Content
		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
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=410108
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.

ID	Field	Content	
32.	Keywords	Female factor fertility problems, infertility, endometrial receptivity array testing, in vitro fertilisation	
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; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; 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 tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Database: Ovid MEDLINE(R) ALL <1946 to April 17, 2023>

Date of last search: 18/04/2023

#	Searches
1	Endometrium/ or uterus/ or (Endometri* or uter*).ti,ab,kf.
2	Gene Expression Profiling/ or Microbiota/ or Microarray Analysis/
3	(gene* adj1 (express* or sequenc* or profil*) adj2 (test or tests or testing or analys*)).ti,ab,kf.
4	(microbio* or micro biome* or microbial biome* or microflora* or micro flora* or (Microarray adj (analys* or test or tests or testing))).ti,ab,kf.
5	(EMMA or ALICE or ERA).ti,ab,kf.
6	or/2-5
7	1 and 6
8	(ERPeakSM or ER Map* or ER Grade* or ER array* or rsERT).ti,ab,kf.
9	((Endometri* or uter*) adj3 receptiv*).ti,ab,kf.
10	or/7-9
11	limit 10 to english language
12	letter/
13	editorial/
14	news/
15	exp historical article/
16	Anecdotes as topic/
17	comment/
18	case reports/
19	(letter or comment*).ti.
20	or/12-19
21	randomized controlled trial/ or random*.ti,ab.
22	20 not 21
23	animals/ not humans/
24	exp Animals, Laboratory/
25	exp Animal Experimentation/
26	exp Models, Animal/
27	exp Rodentia/
28	(rat or rats or rodent* or mouse or mice).ti.
29	or/22-28
30	11 not 29
31	meta-analysis/
32	meta-analysis as topic/
33	(meta analy* or metanaly* or metaanaly*).ti,ab.
34	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
35	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
36	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
37	(search* adj4 literature).ab.
38	(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.
39	cochrane.jw.
40	or/31-39
41	randomized controlled trial.pt.

#	Searches
42	controlled clinical trial.pt.
43	pragmatic clinical trial.pt.
44	randomi#ed.ab.
45	placebo.ab.
46	drug therapy.fs.
47	randomly.ab.
48	trial.ab.
49	groups.ab.
50	or/41-49
51	Clinical Trials as topic.sh.
52	trial.ti.
53	or/41-45,47,51-52
54	30 and 40
55	30 and 53
56	54 or 55
57	limit 56 to ed=20000101-20230418
58	limit 56 to dt=20000101-20230418
59	57 or 58

1 **Database: Embase <1974 to 2023 April 17>**

2 **Date of last search: 18/04/2023**

#	Searches
1	Endometrium/ or uterus/ or (Endometri* or uter*).ti,ab,kf.
2	gene expression profiling/
3	microflora/ or microbiome/
4	microarray analysis/
5	(gene* adj1 (express* or sequenc* or profil*) adj2 (test or tests or testing or analys*)).ti,ab,kf.
6	(microbio* or micro biome* or microbial biome* or microflora* or micro flora* or (Microarray adj (analys* or test or tests or testing))).ti,ab,kf.
7	(EMMA or ALICE or ERA).ti,ab,kf.
8	or/2-7
9	1 and 8
10	(ERPeakSM or ER Map* or ER Grade* or ER array* or rsERT).ti,ab,kf.
11	((Endometri* or uter*) adj3 receptiv*).ti,ab,kf.
12	or/9-11
13	limit 12 to english language
14	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
15	13 not 14
16	letter.pt. or letter/
17	note.pt.
18	editorial.pt.
19	case report/ or case study/
20	(letter or comment*).ti.
21	or/16-20
22	randomized controlled trial/ or random*.ti,ab.
23	21 not 22
24	animal/ not human/
25	nonhuman/
26	exp Animal Experiment/
27	exp Experimental Animal/
28	animal model/
29	exp Rodent/
30	(rat or rats or rodent* or mouse or mice).ti.

#	Searches
31	or/23-30
32	15 not 31
33	systematic review/
34	meta-analysis/
35	(meta analy* or metanaly* or metaanaly*).ti,ab.
36	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39	(search* adj4 literature).ab.
40	(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.
41	((pool* or combined) adj2 (data or trials or studies or results)).ab.
42	cochrane.jw.
43	or/33-42
44	random*.ti,ab.
45	factorial*.ti,ab.
46	(crossover* or cross over*).ti,ab.
47	((doubl* or singl*) adj blind*).ti,ab.
48	(assign* or allocat* or volunteer* or placebo*).ti,ab.
49	crossover procedure/
50	single blind procedure/
51	randomized controlled trial/
52	double blind procedure/
53	or/44-52
54	32 and (43 or 53)
55	limit 54 to dc=20000101-20230418

1 **Database: Cochrane Database of Systematic Reviews Issue 4 of 12, April 2023**

2 **Date of last search: 18/04/2023**

#	Searches
1	MeSH descriptor: [Endometrium] this term only
2	MeSH descriptor: [Uterus] this term only
3	(Endometri* or uter*):ti,ab,kw
4	#1 OR #3
5	MeSH descriptor: [Gene Expression Profiling] this term only
6	MeSH descriptor: [Microbiota] this term only
7	MeSH descriptor: [Microarray Analysis] this term only
8	(gene* NEAR/1 (express* or sequenc* or profil*) NEAR/2 (test or tests or testing or analys*)):ti,ab,kw
9	(microbio* or (micro NEXT biome*) or (microbial NEXT biome*) or microflora* or (micro NEXT flora*) or (Microarray NEXT (analys* or test or tests or testing))):ti,ab,kw
10	(EMMA or ALICE or ERA):ti,ab,kw
11	{or #5-#10}
12	#4 AND #11
13	(ERPeakSM or (ER NEXT Map*) or (ER NEXT Grade*) or (ER NEXT array*) or rsERT):ti,ab,kw
14	((Endometri* or uter*) NEAR/3 receptiv*):ti,ab,kw
15	{or #12-#14}
16	"conference":pt or (clinicaltrials or trialsearch):so
17	#15 NOT #16 with Cochrane Library publication date Between Jan 2000 and Apr 2023, in Cochrane Reviews

3 **Database: Cochrane Central Register of Controlled Trials Issue 4 of 12, April 2023**

4 **Date of last search: 18/04/2023**

#	Searches

#	Searches
1	MeSH descriptor: [Endometrium] this term only
2	MeSH descriptor: [Uterus] this term only
3	(Endometri* or uter*):ti,ab,kw
4	#1 OR #3
5	MeSH descriptor: [Gene Expression Profiling] this term only
6	MeSH descriptor: [Microbiota] this term only
7	MeSH descriptor: [Microarray Analysis] this term only
8	(gene* NEAR/1 (express* or sequenc* or profil*) NEAR/2 (test or tests or testing or analys*)):ti,ab,kw
9	(microbio* or (micro NEXT biome*) or (microbial NEXT biome*) or microflora* or (micro NEXT flora*) or (Microarray NEXT (analys* or test or tests or testing))):ti,ab,kw
10	(EMMA or ALICE or ERA):ti,ab,kw
11	{or #5-#10}
12	#4 AND #11
13	(ERPeakSM or (ER NEXT Map*) or (ER NEXT Grade*) or (ER NEXT array*) or rsERT):ti,ab,kw
14	((Endometri* or uter*) NEAR/3 receptiv*):ti,ab,kw
15	{or #12-#14}
16	"conference":pt or (clinicaltrials or trialsearch):so
17	#15 NOT #16 with Publication Year from 2000 to 2023, in Trials

1 **Database: Epistemonikos**

2 **Date of last search: 18/04/2023**

#	Searches
1	(title:((Endometri* OR uter*) AND (gene* AND (express* OR sequenc* OR profil*) AND (test OR tests OR testing OR analys*))) OR abstract:((Endometri* OR uter*) AND (gene* AND (express* OR sequenc* OR profil*) AND (test OR tests OR testing OR analys*)))) OR (title:((Endometri* OR uter*) AND (microbio* OR (micro AND biome*) OR (microbial AND biome*) OR microflora* OR (micro AND flora*) OR (Microarray AND (analys* OR test OR tests OR testing)) OR EMMA OR ALICE OR ERA)) OR abstract:((Endometri* OR uter*) AND (microbio* OR (micro AND biome*) OR (microbial AND biome*) OR microflora* OR (micro AND flora*) OR (Microarray AND (analys* OR test OR tests OR testing)) OR EMMA OR ALICE OR ERA))) OR (title:(ERPeakSM OR (ER AND Map*) OR (ER AND Grade*) OR (ER AND array*) OR rsERT OR ((Endometri* OR uter*) AND receptiv*)) OR abstract:(ERPeakSM OR (ER AND Map*) OR (ER AND Grade*) OR (ER AND array*) OR rsERT OR ((Endometri* OR uter*) AND receptiv*))) Limit to systematic reviews. Date range 2000-2023

3 **Health Economic Literature search strategies**

4 **Database: Ovid MEDLINE(R) ALL <1946 to April 19, 2023>**

5 **Date of last search: 20/04/2023**

#	Searches
1	Endometrium/ or uterus/ or (Endometri* or uter*).ti,ab,kf.
2	Gene Expression Profiling/ or Microbiota/ or Microarray Analysis/
3	(gene* adj1 (express* or sequenc* or profil*) adj2 (test or tests or testing or analys*)).ti,ab,kf.
4	(microbio* or micro biome* or microbial biome* or microflora* or micro flora* or (Microarray adj (analys* or test or tests or testing))).ti,ab,kf.
5	(EMMA or ALICE or ERA).ti,ab,kf.
6	or/2-5
7	1 and 6
8	(ERPeakSM or ER Map* or ER Grade* or ER array* or rsERT).ti,ab,kf.
9	((Endometri* or uter*) adj3 receptiv*).ti,ab,kf.
10	or/7-9
11	limit 10 to english language
12	letter/
13	editorial/
14	news/

#	Searches
15	exp historical article/
16	Anecdotes as topic/
17	comment/
18	case reports/
19	(letter or comment*).ti.
20	or/12-19
21	randomized controlled trial/ or random*.ti,ab.
22	20 not 21
23	animals/ not humans/
24	exp Animals, Laboratory/
25	exp Animal Experimentation/
26	exp Models, Animal/
27	exp Rodentia/
28	(rat or rats or rodent* or mouse or mice).ti.
29	or/22-28
30	11 not 29
31	Economics/
32	Value of life/
33	exp "Costs and Cost Analysis"/
34	exp Economics, Hospital/
35	exp Economics, Medical/
36	exp Resource Allocation/
37	Economics, Nursing/
38	Economics, Pharmaceutical/
39	exp "Fees and Charges"/
40	exp Budgets/
41	budget*.ti,ab.
42	cost*.ti,ab.
43	(economic* or pharmaco?economic*).ti,ab.
44	(price* or pricing*).ti,ab.
45	(financ* or fee or fees or expenditure* or saving*).ti,ab.
46	(value adj2 (money or monetary)).ti,ab.
47	resourc* allocat*.ti,ab.
48	(fund or funds or funding* or funded).ti,ab.
49	(ration or rations or rationing* or rationed).ti,ab.
50	ec.fs.
51	or/31-50
52	quality-adjusted life years/
53	sickness impact profile/
54	(quality adj2 (wellbeing or well being)).ti,ab.
55	sickness impact profile.ti,ab.
56	disability adjusted life.ti,ab.
57	(qal* or qtime* or qwb* or daly*).ti,ab.
58	(euroqol* or eq5d* or eq 5*).ti,ab.
59	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
60	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
61	(hui or hui1 or hui2 or hui3).ti,ab.
62	(health* year* equivalent* or hye or hyes).ti,ab.
63	discrete choice*.ti,ab.
64	rosser.ti,ab.
65	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
66	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
67	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
68	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.

#	Searches
69	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
70	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
71	or/52-70
72	30 and (51 or 71)
73	limit 72 to yr="2000 -Current"

1 **Database: Embase <1974 to 2023 April 19>**

2 **Date of last search: 20/04/2023**

#	Searches
1	Endometrium/ or uterus/ or (Endometri* or uter*).ti,ab,kf.
2	gene expression profiling/
3	microflora/ or microbiome/
4	microarray analysis/
5	(gene* adj1 (express* or sequenc* or profil*) adj2 (test or tests or testing or analys*)).ti,ab,kf.
6	(microbio* or micro biome* or microbial biome* or microflora* or micro flora* or (Microarray adj (analys* or test or tests or testing))).ti,ab,kf.
7	(EMMA or ALICE or ERA).ti,ab,kf.
8	or/2-7
9	1 and 8
10	(ERPeakSM or ER Map* or ER Grade* or ER array* or rsERT).ti,ab,kf.
11	((Endometri* or uter*) adj3 receptiv*).ti,ab,kf.
12	or/9-11
13	limit 12 to english language
14	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
15	13 not 14
16	letter.pt. or letter/
17	note.pt.
18	editorial.pt.
19	case report/ or case study/
20	(letter or comment*).ti.
21	or/16-20
22	randomized controlled trial/ or random*.ti,ab.
23	21 not 22
24	animal/ not human/
25	nonhuman/
26	exp Animal Experiment/
27	exp Experimental Animal/
28	animal model/
29	exp Rodent/
30	(rat or rats or rodent* or mouse or mice).ti.
31	or/23-30
32	15 not 31
33	health economics/
34	exp economic evaluation/
35	exp health care cost/
36	exp fee/
37	budget/
38	funding/
39	resource allocation/
40	budget*.ti,ab.
41	cost*.ti,ab.
42	(economic* or pharmaco?economic*).ti,ab.
43	(price* or pricing*).ti,ab.

#	Searches
44	(financ* or fee or fees or expenditure* or saving*).ti,ab.
45	(value adj2 (money or monetary)).ti,ab.
46	resourc* allocat*.ti,ab.
47	(fund or funds or funding* or funded).ti,ab.
48	(ration or rations or rationing* or rationed).ti,ab.
49	or/33-48
50	quality adjusted life year/
51	"quality of life index"/
52	short form 12/ or short form 20/ or short form 36/ or short form 8/
53	sickness impact profile/
54	(quality adj2 (wellbeing or well being)).ti,ab.
55	sickness impact profile.ti,ab.
56	disability adjusted life.ti,ab.
57	(qal* or qtime* or qwb* or daly*).ti,ab.
58	(euroqol* or eq5d* or eq 5*).ti,ab.
59	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
60	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
61	(hui or hui1 or hui2 or hui3).ti,ab.
62	(health* year* equivalent* or hye or hyes).ti,ab.
63	discrete choice*.ti,ab.
64	rosser.ti,ab.
65	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
66	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
67	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
68	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
69	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
70	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
71	or/50-70
72	32 and (49 or 71)
73	limit 72 to yr="2000 -Current"

1 Database: HTA via CRD

2 Date of last search: 20/04/2023

#	Searches
1	MeSH DESCRIPTOR endometrium IN HTA
2	MeSH DESCRIPTOR uterus IN HTA
3	((Endometri* or uter*)) IN HT
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR Gene Expression Profiling IN HTA
6	MeSH DESCRIPTOR Microbiota IN HTA
7	MeSH DESCRIPTOR Microarray Analysis IN HTA
8	((gene* adj1 (express* or sequenc* or profil*) adj2 (test or tests or testing or analys*))) IN HTA
9	((microbio* or micro biome* or microbial biome* or microflora* or micro flora* or (Microarray adj (analys* or test or tests or testing)))) IN HTA
10	((EMMA or ALICE or ERA)) IN HTA
11	#5 OR #6 OR #7 OR #8 OR #9 OR #10
12	#4 AND #11
13	((ERPeakSM or ER Map* or ER Grade* or ER array* or rsERT)) IN HTA
14	(((Endometri* or uter*) adj3 receptiv*)) IN HTA
15	#12 OR #13 OR #14

1 **Database: INAHTA**

2 **Date of last search: 20/04/2023**

#	Searches
1	"Endometrium"[mh]
2	"Uterus"[mh]
3	(Endometri* or uter*)
4	#3 OR #2 OR #1
5	"Gene Expression Profiling"[mh]
6	"Microbiota"[mh]
7	"Microarray Analysis"[mh]
8	(gene* and (express* or sequenc* or profil*) and (test or tests or testing or analys*))
9	(microbio* or micro biome* or microbial biome* or microflora* or micro flora* or (Microarray and (analys* or test or tests or testing)))
10	(EMMA or ALICE or ERA)
11	(ERPeakSM or ER Map* or ER Grade* or ER array* or rsERT)
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
13	#12 AND #4
14	((Endometri* or uter*) and receptiv*)
15	#14 OR #13

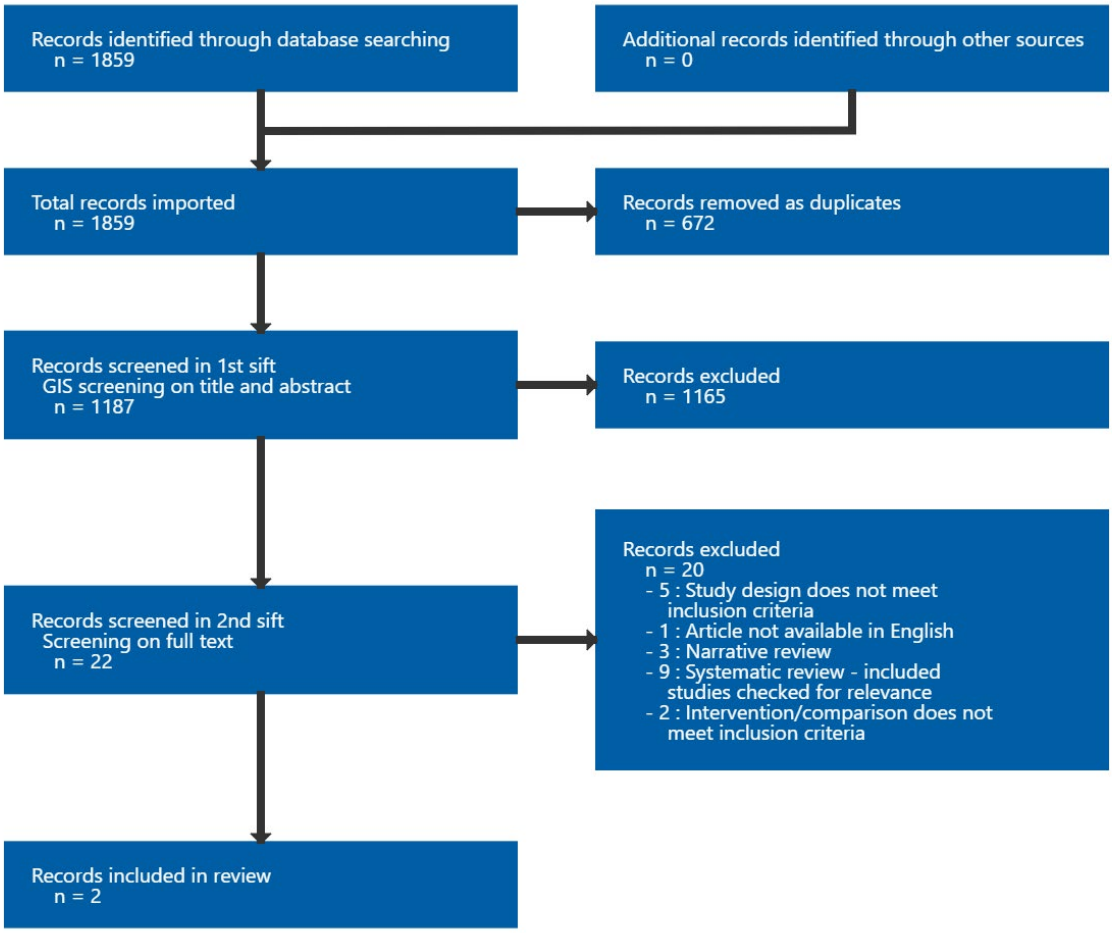
3

4

Appendix C Effectiveness evidence study selection

Study selection for: What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Doyle, 2022

Bibliographic Reference Doyle, Nicole; Jahandideh, Samad; Hill, Micah J; Widra, Eric A; Levy, Michael; Devine, Kate; Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization: A Randomized Clinical Trial.; JAMA; 2022; vol. 328 (no. 21); 2117-2125

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	May 2018 - August 2021
Inclusion criteria	People aged 30-40 years at time of egg retrieval who: • Were planning IVF, preimplantation genetic testing for aneuploidy, and frozen embryo transfer • Were likely to produce ≥1 euploid blastocyst based on ovarian reserve testing • Had ≥1 euploid blastocyst available for embryo transfer • Met standard eligibility criteria to undergo IVF and FET at Shady Grove Fertility Center
Exclusion criteria	• Surgically aspirated sperm or donor egg(s) • Recurrent implantation failure (defined as >2 embryo transfers not resulting in ongoing pregnancy since the participant's last live birth, if any) • Recurrent pregnancy loss (defined as ≥2 clinical pregnancy losses without live birth) • Preimplantation genetic testing for monogenic disorders or structural rearrangements • Unmitigated uterine cavity defect (defined as normal uterine cavity on saline sonogram or hysterosalpingogram was required) • Body mass index >40 kg/m2 at the start of IVF cycle • Current pregnancy or breastfeeding

	• Any contraindication to IVF or pregnancy Participants with no blastocyst available for biopsy or only aneuploid embryos by preimplantation genetic testing were withdrawn prior to randomization.
Patient characteristics	N=767 people undergoing frozen embryo transfer (N=755 completed study) Receptivity-timed frozen embryo transfer group (n=381; n=375 completed study): • Mean age (SD): 34.7 (2.7) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • History of failed embryo transfer/s: 32 (9%) • History of live birth/s: 67 (18%) Standard frozen embryo transfer group (n=386; n=380 completed study): • Mean age (SD): 34.5 (2.7) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • History of failed embryo transfer/s: 26 (7%) • History of live birth/s: 66 (17%)

Intervention(s)/control	Receptivity-timed frozen embryo transfer:
	
	• IVF with single euploid frozen embryo transfer as recommended by endometrial receptivity results (using ERA):
	  ○ If the result was receptive, transfer was performed at standard timing
	  ○ If the result was nonreceptive, relative to standard timing, transfer was performed:
	  ▪ 12 hours earlier if result was late receptive
	  ▪ 12 hours later if the result was early receptive
	  ▪ 24 hours earlier if the result was post-receptive

	▪ 24 or more hours later if the result was pre-receptive (the specific recommended adjustment ranged from 24-48 hours later for pre-receptive results) Standard frozen embryo transfer: • IVF with single euploid frozen embryo transfer 123 ± 3 hours after initiation of progesterone (standard timing) Participants in both groups received the following: • Exogenous estradiol, plus once endometrial thickness reached ≥7 mm with serum progesterone <1.5 ng/mL, either 50 mg of intramuscular progesterone daily or 50 mg of intramuscular progesterone every third day, plus 200 mg twice daily of Endometrin • Endometrial pipelle biopsy for endometrial receptivity testing 123 ± 3 hours after the first progesterone injection, plus repeat testing if endometrial receptivity results were noninformative • The same luteal support regimen as during their endometrial receptivity cycle • Continuation of exogenous estradiol and progesterone for participants with appropriate pregnancy development until 10 weeks' estimated gestational age.
Duration of follow-up	Participants with appropriate pregnancy development were followed up until delivery. Clinical pregnancy was defined as the presence of gestational sac/s at 5-7 weeks' estimated gestational age.
Sources of funding	Funded by Shady Grove Fertility, a private practice. One of the authors received personal fees from Thread Robotics, a medical organisation providing devices and services with a focus on fertility care. One of the authors reported serving on the scientific advisory board of Igenomix, the company commercialising the ERA test.
Sample size	N=767 people undergoing frozen embryo transfer (N=755 completed study): • Receptivity-timed frozen embryo transfer group: n=381 (n=375 completed study) • Standard frozen embryo transfer group: n=386 (n=380 completed study)
Other information	Biochemical pregnancy rates (defined in study as detection of β-hCG level >5 IU/L) were reported but not extracted, as

	clinical pregnancy rates were prioritised. The authors reported results for both intention to treat and per-protocol analyses; results as per the intention to treat analysis were prioritised for extraction.

Outcome	Receptivity-timed frozen embryo transfer group, N = 381	Standard frozen embryo transfer group, N = 386
Live birth Defined in study as live birth at 23 weeks' gestation or beyond.	n = 223 ; % = 58.5	n = 239 ; % = 61.9
Clinical pregnancy at 5-7 weeks Defined in study as presence of gestational sac/s (following transfer of a single euploid blastocyst) on transvaginal ultrasound at 5-7 weeks' estimated gestational age.	n = 262 ; % = 68.8	n = 281 ; % = 72.8
Miscarriage (total pregnancy loss) Reported in study as including biochemical pregnancy loss (initial positive β-hCG that did not progress to clinical pregnancy) and clinical pregnancy loss (clinical pregnancy not progressing to live birth, excluding ectopic pregnancies, therapeutic abortions, and stillbirth).	n = 65 ; % = 17.1	n = 66 ; % = 17.1
Miscarriage (clinical pregnancy loss) Defined in study as clinical pregnancy not progressing to live birth.	n = 36 ; % = 9.4	n = 41 ; % = 10.6
Miscarriage (biochemical pregnancy loss) Defined in study as initial positive β-hCG that did not progress to clinical pregnancy.	n = 29 ; % = 7.6	n = 25 ; % = 6.5
Ectopic pregnancy	n = 3 ; % = 0.8	n = 1 ; % = 0.3
Pregnancy loss Including: total pregnancy loss (biochemical or clinical pregnancy loss); ectopic pregnancy; stillbirth; therapeutic abortion.	n = 71 ; % = 18.6	n = 68 ; % = 1.8

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Balanced (1:1) randomization was performed for participants with euploid embryo(s) and an informative endometrial receptivity report, using generated sequential lists of randomized group assignments by the method of randomly*

Section	Question	Answer
		permutated blocks of random block size using an internet-based randomization program (http://www. randomization.com). The assignment was revealed only to the study coordinators by opening a sequentially numbered, sealed, opaque envelope.)
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)	Low *(Double blind trial whereby both groups received endometrial receptivity testing. Endometrial receptivity cycle results were received only by the study coordinators and not disclosed to the patient or clinical team. Although the physician, nurse, and patient might have been able to deduce assignment based on the frozen embryo transfer time if the progesterone exposure time prior to frozen embryo transfer was other than 123 ± 3 hours, potential bias was minimised because they were not able to access receptivity results or randomisation group, and the study team assigned progesterone start and frozen embryo transfer times (calculated based on the patient's study group). The assessor (statistician) remained blinded throughout.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Six participants in each group (2% of intervention group and 2% of control group) were withdrawn from the study post-randomisation. 2 participants in each group were withdrawn prior to frozen embryo transfer; 4 participants in the intervention group were withdrawn after the completed transfer (2 for endometrial receptivity cycle protocol violation whereby a transcription error resulted in miscalculation of progesterone exposure time prior to transfer for participant with nonreceptive results; 2 for frozen embryo transfer protocol violation whereby the progesterone start time was not followed according to randomization group); 4 participants in the control group were withdrawn after the completed transfer (all for endometrial receptivity cycle protocol violation: 2 whereby the progesterone start time was not followed; 1 whereby the participant was randomized to the standard transfer but underwent a receptivity-guided transfer; 1 whereby the patient had a medication violation). Results are presented for all randomised participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Methods for assessing the outcomes were appropriate and were based on measurements/ definitions that would have minimised the potential for*

Section	Question	Answer
		differences between groups. Outcome assessors were blinded to the intervention, although the physician, nurse, and patient might have been able to deduce assignment based on the frozen embryo transfer time if the progesterone exposure time prior to frozen embryo transfer was other than 123 ± 3 hours. Assessment of all outcomes is unlikely to have been influenced by knowledge of intervention received.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Protocol available on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT03558399), published in June 2018 and last updated December 2020 after enrollment was concluded (enrollment took place from May 2018 to September 2020). Data analysed in accordance with the pre-specified analysis plan and all analyses reported (intention to treat and per-protocol). The outcome ongoing pregnancy (defined as viable pregnancy at 8-10 weeks' gestation) was initially analysed as a proxy for live birth after the final study visit had been completed but before the final live birth outcome was known, but was not reported because this analysis was replaced with the more relevant planned primary outcome live birth.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable. Participants did not explicitly have a health-related fertility problem but received tests for endometrial receptivity as an add-on to ART (IVF).
Overall bias and Directness	Risk of bias variation across outcomes	None.

1 **Simon, 2020**

Bibliographic Reference Simon, Carlos; Gomez, Carlos; Cabanillas, Sergio; Vladimirov, Iavor; Castillon, Gemma; Giles, Juan; Boynukalin, Kubra; Findikli, Necati; Bahceci, Mustafa; Ortega, Israel; Vidal, Carmina; Funabiki, Miyako; Izquierdo, Alexandra; Lopez, Lourdes; Portela, Susana; Frantz, Nilo; Kulmann, Marcos; Taguchi, Sagiri; Labarta, Elena; Colucci, Francisco; Mackens, Shari; Santamaria, Xavier; Munoz, Elkin; Barrera, Saul; Garcia-Velasco, Juan Antonio; Fernandez, Manuel; Ferrando, Marcos; Ruiz, Maria; Mol, Ben W; Valbuena, Diana; A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF.; Reproductive biomedicine online; 2020; vol. 41 (no. 3); 402-415

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3 Study details

Country/ies where study was carried out	16 reproductive clinics in Europe, USA and Asia
Study type	Randomised controlled trial (RCT)
Study dates	November 2013 to April 2017.
Inclusion criteria	Infertile women undergoing IVF and scheduled for embryo transfer at the blastocyst stage (day 5 or 6), who: • Were aged ≤37 years • Had a BMI of 18.5 - 30 • Had a normal ovarian reserve (antral follicle count ≥8 and FSH <8 IU/ml)
Exclusion criteria	• Recurrent miscarriage (>2 previous biochemical pregnancies or spontaneous miscarriages) • Previous implantation failure (>3 failed IVF cycles with good quality embryos transferred) • Severe male factor infertility in the male partner (spermatozoa <2 x10^6/ml) Post-randomisation exclusion criteria included: • Progesterone levels >1.5 ng/ ml on the day of HCG administration in all groups • Absence of blastocysts (day 5 or 6) for embryo transfer in the fresh embryo transfer arm only • Risk of ovarian hyperstimulation syndrome (OHSS) in any group and therefore a clinical indication to cancel the transfer cycle in the fresh embryo transfer group.
Patient characteristics	N=458 infertile women undergoing IVF (N=434 participants included in analysis (n=24 lost to follow-up)): Personalised embryo transfer group (n=148; n=141 included in analysis): • Mean age (SD): 33 (3.1) years • Previous implantation failure: 0 (people with recurrent implantation failure were excluded) • Previous IVF failure: ○ No previous failed IVF: 109 (74%)

- 1 previous failed IVF: 20 (14%)
- 2 previous failed IVF: 10 (7%)
- 3 previous failed IVF: 6 (4%)
- Unknown: 3 (2%)

- History of live birth/s:
  - 1 previous delivery: 11 (7%)
  - ≥2 previous deliveries: 3 (2%)
- Transfers:
  - Mean embryos per transfer (SD): 1.52 (0.5)
  - Cumulative number of transfers*: 282

Frozen embryo transfer group (n=154; n=148 included in analysis):

- Mean age (SD): 32.8 (3.4) years
- Previous implantation failure: 0 (people with recurrent implantation failure were excluded)
- Previous IVF failure:
  - No previous failed IVF: 104 (68%)
  - 1 previous failed IVF: 23 (15%)
  - 2 previous failed IVF: 10 (7%)
  - 3 previous failed IVF: 11 (7%)
  - Unknown: 6 (4%)
- History of live birth/s:
  - 1 previous delivery: 16 (10%)
  - ≥2 previous deliveries: 4 (3%)
- Transfers:
  - Mean embryos per transfer (SD): 1.61 (0.5)
  - Cumulative number of transfers*: 267

Fresh embryo transfer group (n=156; n=145 included in analysis):

- Mean age (SD): 32.7 (3.3) years

	• Previous implantation failure: 0 (people with recurrent implantation failure were excluded)
	• Previous IVF failure:
	  ○ No previous failed IVF: 112 (72%)
	  ○ 1 previous failed IVF: 22 (14%)
	  ○ 2 previous failed IVF: 12 (8%)
	  ○ 3 previous failed IVF: 6 (4%)
	  ○ Unknown: 4 (3%)
	• History of live birth/s:
	  ○ 1 previous delivery: 17 (11%)
	  ○ ≥2 previous deliveries: 3 (2%)
	• Transfers:
	  ○ Mean embryos per transfer (SD): 1.63 (0.5)
	  ○ Cumulative number of transfers*: 248
	
	*Cumulative number of transfers includes all embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period

Intervention(s)/control	Personalised embryo transfer: • 1 or 2 endometrial biopsies (the timing of the second biopsy depended on the result of the first) were collected from the uterine fundus for ERA test • Properly developed blastocysts were vitrified using different protocols depending on the IVF laboratory • Embryo transfer was carried out in an HRT cycle at the timing indicated by the ERA test Frozen embryo transfer: • Properly developed blastocysts were vitrified using different protocols depending on the IVF laboratory • Frozen embryo transfer was carried out in an HRT cycle. Further information about the timing is not reported • Patients received transfer during a hormonal replacement therapy cycle after embryo thawing, following the protocol and timing used in each clinic

	Fresh embryo transfer: • Embryo transfer was carried out 5 or 6 days after oocyte retrieval according to blastocyst timing • Luteal phase supplementation route and dosage were determined by the participant physician or clinic Participants in all groups received the following: • Ovarian stimulation using standard protocols in each of the participant sites according to female age, basal hormone levels, basal ovarian reserve and BMI • ICSI or IVF according to the protocols of the participating sites
Duration of follow-up	Not reported. Follow-up for all outcomes took place after the first embryo transfer.
Sources of funding	Industry funded: the primary author is the co-inventor of the ERA patent, Head of the Scientific Advisory Board of Igenomix (the company commercializing the ERA test) and holds shares in Igenomix. The study was sponsored by Igenomix. Multiple authors are employees of Igenomix SL. One author reports a grant (GNT1082548) from the Australian National Health and Medical Research Council (NHMRC) related to the submitted work.
Sample size	N=458 women undergoing IVF (N=434 participants included in analysis): • Personalised embryo transfer group: n=148 (n=141 included in analysis) • Frozen embryo transfer group: n=154 (n=148 included in analysis) • Fresh embryo transfer group: n=156 (n=145 included in analysis)
Other information	Cumulative outcomes were reported in the study per total number of patients receiving additional embryo transfer following the same type of transfer arm into which the patient was randomized for up to 12 months' follow-up. These outcomes included all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period. The authors reported results for modified intention to treat (excluding those lost to follow-up) and per-protocol analyses; results as per the modified intention to treat analysis were prioritised for extraction.

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Outcome (per participant)	Personalised embryo transfer group, N = 141	Frozen embryo transfer group, N = 148	Fresh embryo transfer group, N = 145
Live birth Reported in study as live birth rate: the number of deliveries that resulted in at least one live birth. Live birth is defined in the study as the complete expulsion or extraction from a woman of a product of conception after 22 weeks of gestation, which, after such separation, breathes or shows any other evidence of life, such as heart beat, umbilical cord pulsation or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached.	n = 57 ; % = 40.4	n = 51 ; % = 34.5	n = 64 ; % = 44.1
Cumulative live birth at 12 months Including from all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period.	n = 88 ; % = 62.4	n = 82 ; % = 55.4	n = 85 ; % = 58.6
Clinical pregnancy at 5 weeks Reported in the study as pregnancy rate and defined as the number of patients with positive serum level of β-hCG (≥25 mIU/ml). Biochemical pregnancies without progression to clinical pregnancy are included in this outcome in the reported results (PET group: n=7/83; FET group: n=9/73; frozen ET group: n=11/84), but have been excluded during extraction. Therefore only the number of pregnancies with a gestational sac visualized by vaginal ultrasound at the fifth week of pregnancy have been extracted.	n = 76 ; % = 53.9	n = 64 ; % = 43.2	n = 73 ; % = 50.3
Cumulative clinical pregnancy at 12 months Including participants with clinical pregnancy from all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period. Biochemical pregnancies are included in this outcome in the reported results (PET group: n=19/132; FET group: n=16/118; frozen ET group: n=23/117), but have been excluded during extraction. Therefore only the number of pregnancies with a gestational sac visualized by vaginal ultrasound at the fifth week of pregnancy have been extracted.	n = 132 ; % = 93.6	n = 118 ; % = 79.8	n = 117 ; % = 80.7

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Outcome (per pregnancy)	Personalised embryo transfer group, N = 83	Frozen embryo transfer group, N = 73	Fresh embryo transfer group, N = 84

Outcome (per pregnancy)	Personalised embryo transfer group, N = 83	Frozen embryo transfer group, N = 73	Fresh embryo transfer group, N = 84
Miscarriage (total pregnancy loss) Reported in study as including biochemical pregnancies (the number of pregnancies diagnosed only by β-hCG detection without a gestational sac visualized by vaginal ultrasound at the fifth week of pregnancy) and clinical pregnancy loss (the number of spontaneous pregnancy losses in which a gestational sac or sacs was previously observed), per number of pregnancies	n = 24 ; % = 28.9	n = 20 ; % = 27.4	n = 16 ; % = 19
Miscarriage (clinical pregnancy loss) Reported in study as the number of spontaneous pregnancy losses in which a gestational sac or sacs was previously observed, per number of pregnancies.	n = 17 ; % = 20.5	n = 11 ; % = 15.1	n = 5 ; % = 6
Miscarriage (biochemical pregnancy) Reported in study as the number of pregnancies diagnosed only by β-hCG detection without a gestational sac visualized by vaginal ultrasound at the fifth week of pregnancy, per number of pregnancies.	n = 7 ; % = 8.4	n = 9 ; % = 12.3	n = 11 ; % = 13.1
Ectopic pregnancy Defined in the study as the number of pregnancies outside the uterine cavity, diagnosed by ultrasound, surgical visualization or histopathology, per number of pregnancies.	n = 1 ; % = 1.2	n = 1 ; % = 1.4	n = 1 ; % = 1.2
Pregnancy loss Including: total pregnancy loss (biochemical pregnancies or clinical pregnancy loss); ectopic pregnancy; elective termination of pregnancy.	n = 26 ; % = 31.3	n = 21; % = 28.8	n = 18 ; % = 21.4

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Outcome (per pregnancy, including all subsequent embryo transfers within 1 year follow-up)	Personalised embryo transfer group, N = 132	Frozen embryo transfer group, N = 118	Fresh embryo transfer group, N = 117
Cumulative miscarriage (total pregnancy loss) at 12 months Reported in study as including biochemical pregnancies and clinical pregnancy loss per pregnancy, including from all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period.	n = 43 ; % = 32.6	n = 33 ; % = 28	n = 28 ; % = 23.9
Cumulative miscarriage (clinical pregnancy loss) at 12 months Reported in study as the number of spontaneous pregnancy losses per number of	n = 24 ; % = 18.2	n = 17 ; % = 14.4	n = 5 ; % = 4.3

Outcome (per pregnancy, including all subsequent embryo transfers within 1 year follow-up)	Personalised embryo transfer group, N = 132	Frozen embryo transfer group, N = 118	Fresh embryo transfer group, N = 117
pregnancies, including from all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period.			
Cumulative miscarriage (biochemical pregnancies) at 12 months Reported in study as the number of biochemical pregnancies per number of pregnancies, including from all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period.	n = 19 ; % = 14.4	n = 16 ; % = 13.6	n = 23 ; % = 19.7
Cumulative ectopic pregnancy at 12 months Defined in the study as the number of pregnancies outside the uterine cavity per number of pregnancies, including all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period.	n = 1 ; % = 0.8	n = 1 ; % = 0.8	n = 1 ; % = 0.9
Cumulative pregnancy loss at 12 months Including: total pregnancy loss (biochemical pregnancies or clinical pregnancy loss); ectopic pregnancy; elective termination of pregnancy, including from all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period.	n = 45 ; % = 34.1	n = 34 ; % = 28.8	n = 30 ; % = 25.6

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Outcome (per live birth)	Personalised embryo transfer group, N = 57	Frozen embryo transfer group, N = 51	Fresh embryo transfer group, N = 64
Multiple gestation Reported in study as number of multiple live births; number of multiple pregnancies is not reported. All instances of multiple live births were twins.	n = 8 ; % = 14	n = 11 ; % = 21.6	n = 19 ; % = 29.7

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Outcome (per live birth, including from all subsequent embryo transfers within 1 year follow-up)	Personalised embryo transfer group, N = 88	Frozen embryo transfer group, N = 82	Fresh embryo transfer group, N = 85
Cumulative multiple gestation at 12 months	n = 13 ; % = 14.8	n = 15 ; % = 18.3	n = 27 ; % =

Outcome (per live birth, including from all subsequent embryo transfers within 1 year follow-up)	Personalised embryo transfer group, N = 88	Frozen embryo transfer group, N = 82	Fresh embryo transfer group, N = 85
Reported in study as number of multiple live births, including from all subsequent embryo transfers carried out within 1 year after the first embryo transfer carried out during the study period; number of multiple pregnancies is not reported. All instances of multiple live births were twins.			31.8

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2 Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was done using a simple equal probability randomization method. A software-based application was used to allocate intervention (1:1:1) with randomization stratified by site.)*
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 *(The trial was non-blinded. There were deviations from the intended intervention, for those that did not receive blastocyst transfer (n=27), it is unlikely that this was due to the trial context: 16 had no blastocyst; 6 spontaneous pregnancies occurred; 2 were cancelled due to OHSS risk; in 3 cases, no embryo transfer data were found. However, 139 participants did not fully comply with the protocol (7 participants in the PET group had no PET; 6 in the non-PET groups had PET; 10 and 7 had fresh and frozen embryo transfer respectively in the PET group; 22 had fresh embryo transfer in the FET group; 6 had frozen embryo transfer in the embryo transfer group; 13 had frozen embryo transfer owing to OHSS risk in the fresh embryo transfer group; 43 had high progesterone; 21 had fresh embryo transfer on day 2, 3 or 4; 4 protocol deviations for other reasons not reported). It is unclear whether the participants who did not receive their assigned interventions did so because of the trial context. Additionally, participants in the PET group received more cumulative transfers than participants in either of the other groups, although the authors have argued that the total number of embryo transfers per arm did not statistically differ <https://www.rbmojournal.com/article/S1472-6483(20)30533-2/fulltext>. The number of participants included in the per-protocol analysis is balanced between groups, and an intention to treat analysis was also conducted.)*
Domain 3. Bias due to	Risk-of-bias judgement for	Low

Section	Question	Answer
missing outcome data	missing outcome data	*(24 participants (5%) were lost to follow-up. The number of participants lost to follow-up in each group was comparable (PET group: 7/148 (5%); FET group: 6/154 (4%); fresh ET group: 11/156 (7%)).)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Methods for assessing the outcomes were appropriate and were based on measurements/ definitions that would have minimised the potential for differences between groups. Outcome assessors were not blinded to the intervention, but assessment of all outcomes is unlikely to have been influenced by knowledge of intervention received.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Protocol available on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01954758), published in October 2013 before the trial started and last updated February 2019 after the study was concluded (the study was conducted from November 2013 to April 2017). The trial was amended from a single-blind, 5-arm study, with a recruitment target of 2442 to an unblinded, 3-arm study in 458 women due to difficulties with recruitment. It is unclear why the number of arms was amended. Additionally, the cumulative clinical pregnancy and cumulative live birth outcomes were added retrospectively to the protocol in February 2019, after the study had concluded. The other cumulative outcomes (cumulative clinical pregnancy loss, cumulative biochemical pregnancy, cumulative ectopic pregnancy, and cumulative multiple gestation) are not listed in the protocol.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding deviations from the intended interventions and selection of the reported result.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	High risk of bias for cumulative outcomes due to selection of the reported result.

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Appendix E Forest plots

Forest plots for review question: What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Figure 2: ERT-timed FET vs standard FET, live birth

Figure 3: ERT-timed FET vs standard FET, clinical pregnancy at 5-7 weeks

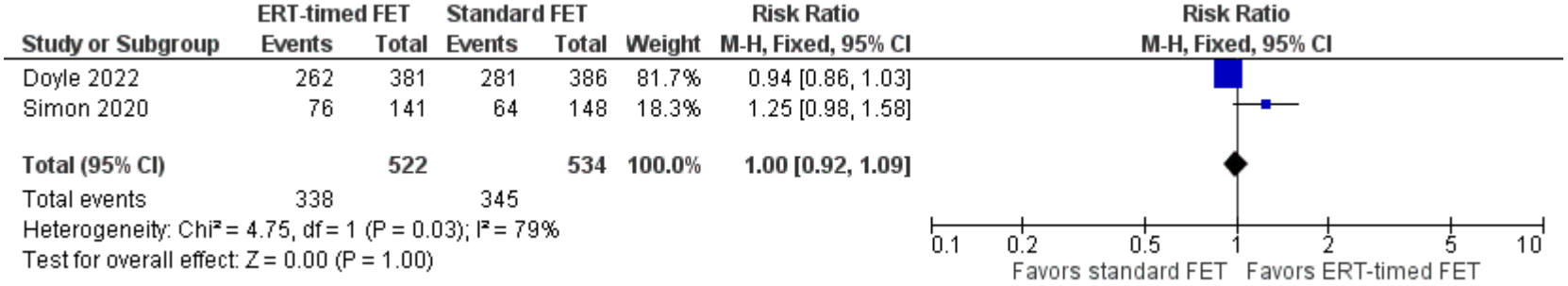
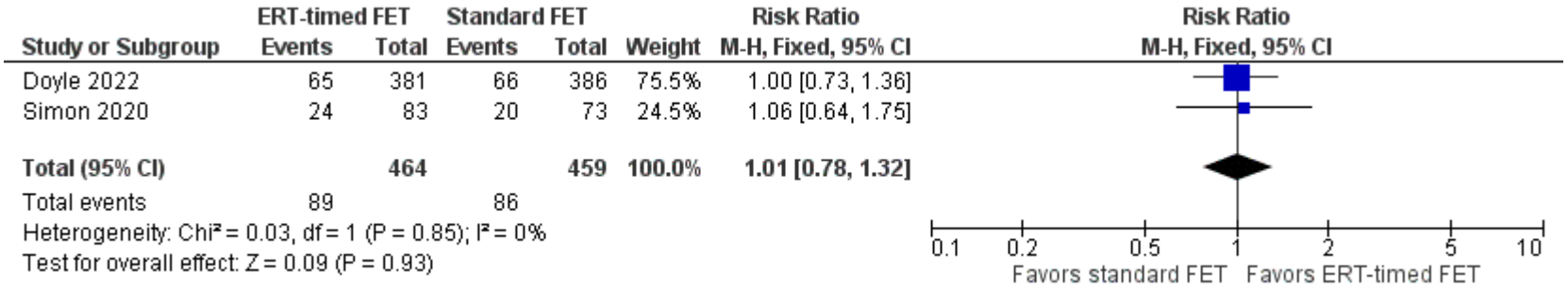
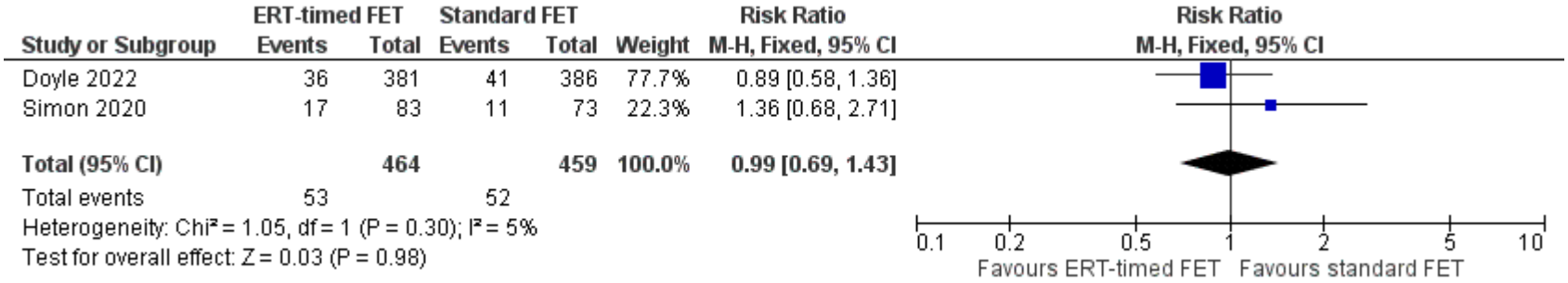


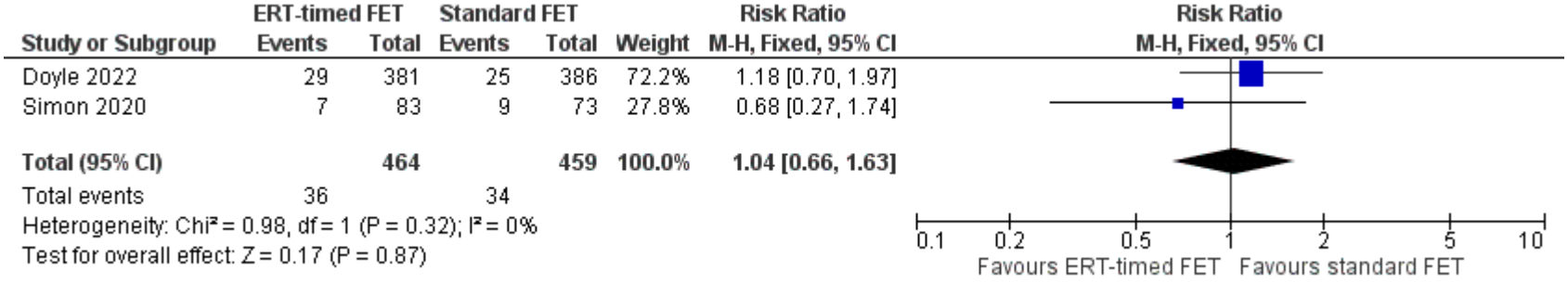
Figure 4: ERT-timed FET vs standard FET, miscarriage (total pregnancy loss)



1 **Figure 5: ERT-timed FET vs standard FET, miscarriage (clinical pregnancy loss)**



2 **Figure 6: ERT-timed FET vs standard FET, miscarriage (biochemical pregnancy loss)**



3 **Figure 7: ERT-timed FET vs standard FET, ectopic pregnancy**

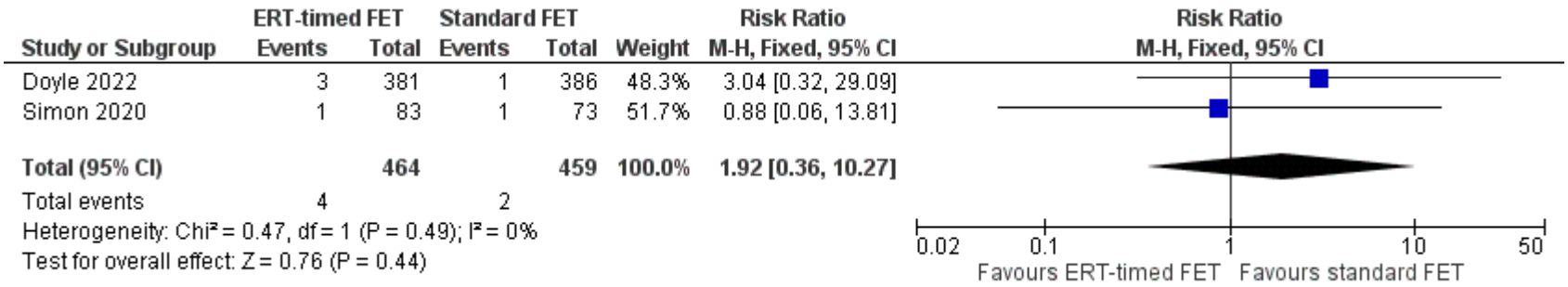
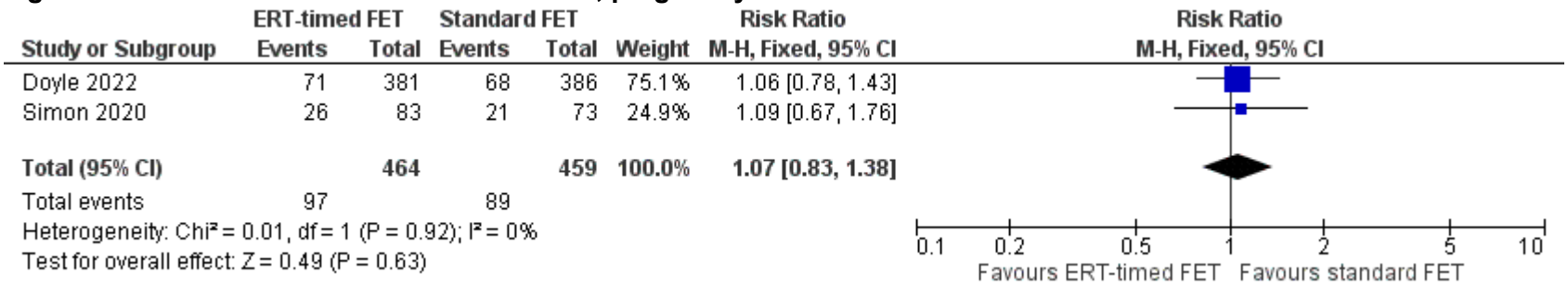


Figure 8: ERT-timed FET vs standard FET, pregnancy loss



Appendix F GRADE tables

GRADE tables for review question: What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Table 5: Evidence profile for comparison between ERA-timed FET vs standard FET

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ERT-timed FET	Standard FET	Relative (95% CI)	Absolute		
Live birth												
2[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	280/522 (53.6%)	290/534 (54.3%)	RR 0.98 (0.88 to 1.1)	11 fewer per 1000 (from 65 fewer to 54 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cumulative live birth at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[3]	88/141 (62.4%)	82/148 (55.4%)	RR 1.13 (0.93 to 1.37)	72 more per 1000 (from 39 fewer to 205 more)	⊕OOO VERY LOW	CRITICAL
Clinical pregnancy at 5-7 weeks												
2[a]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	338/522 (64.8%)	345/534 (64.6%)	RR 1 (0.92 to 1.09)	0 fewer per 1000 (from 52 fewer to 58 more)	⊕⊕⊕O MODERATE	CRITICAL
Cumulative clinical pregnancy at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	132/141 (93.6%)	118/148 (79.7%)	RR 1.17 (1.07 to 1.29)	136 more per 1000 (from 56 more to 231 more)	⊕OOO VERY LOW	CRITICAL
Miscarriage (total pregnancy loss)												
2[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	89/464 (19.2%)	86/459 (18.7%)	RR 1.01 (0.78 to 1.32)	2 more per 1000 (from 41 fewer to 60 more)	⊕⊕OO LOW	IMPORTANT
Cumulative miscarriage (total pregnancy loss) at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	43/132 (32.6%)	33/118 (28%)	RR 1.16 (0.8 to 1.7)	45 more per 1000 (from 56 fewer to 196 more)	⊕OOO VERY LOW	IMPORTANT
Miscarriage (clinical pregnancy loss)												
2[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	53/464 (11.4%)	52/459 (11.3%)	RR 0.99 (0.69 to 1.43)	1 fewer per 1000 (from 35 fewer to 49 more)	⊕⊕OO LOW	IMPORTANT
Cumulative miscarriage (clinical pregnancy loss) at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[3]	24/132 (18.2%)	17/118 (14.4%)	RR 1.26 (0.71 to 2.23)	37 more per 1000 (from 42 fewer to 177 more)	⊕OOO VERY LOW	IMPORTANT
Miscarriage (biochemical pregnancy loss)												

2[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	36/464 (7.8%)	34/459 (7.4%)	RR 1.04 (0.66 to 1.63)	3 more per 1000 (from 25 fewer to 47 more)	⊕⊕OO LOW	IMPORTANT
Cumulative miscarriage (biochemical pregnancy loss) at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[3]	19/132 (14.4%)	16/118 (13.6%)	RR 1.06 (0.57 to 1.97)	8 more per 1000 (from 58 fewer to 132 more)	⊕OOO VERY LOW	IMPORTANT
Ectopic pregnancy												
2[a]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[3]	4/464 (0.86%)	2/459 (0.44%)	RR 1.92 (0.36 to 10.27)	4 more per 1000 (from 3 fewer to 40 more)	⊕OOO VERY LOW	IMPORTANT
Cumulative ectopic pregnancy at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[3]	1/132 (0.76%)	1/118 (0.85%)	RR 0.89 (0.06 to 14.13)	1 fewer per 1000 (from 8 fewer to 111 more)	⊕OOO VERY LOW	IMPORTANT
Pregnancy loss												
2[a]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	97/464 (20.9%)	89/459 (19.4%)	RR 1.07 (0.83 to 1.38)	14 more per 1000 (from 33 fewer to 74 more)	⊕⊕⊕O MODERATE	IMPORTANT
Cumulative pregnancy loss at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	45/132 (34.1%)	34/118 (28.8%)	RR 1.18 (0.82 to 1.71)	52 more per 1000 (from 52 fewer to 205 more)	⊕OOO VERY LOW	IMPORTANT
Multiple gestation												
1 (Simon 2020)	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[3]	8/57 (14%)	11/51 (21.6%)	RR 0.65 (0.28 to 1.49)	75 fewer per 1000 (from 155 fewer to 106 more)	⊕OOO VERY LOW	IMPORTANT
Cumulative multiple gestation at 12 months												
1 (Simon 2020)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[3]	13/88 (14.8%)	15/82 (18.3%)	RR 0.81 (0.41 to 1.59)	35 fewer per 1000 (from 108 fewer to 108 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence intervals; ERA: Endometrial Receptivity Array; FET: frozen embryo transfer; LoNE: line of no effect; MID: minimally important difference; RoB: risk of bias; RR: risk ratio

a Doyle 2022, Simon 2020

[1] <300 events

[2] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[3] Publication bias suspected due to study with the most weight being industry funded by the company commercializing the ERA test and the author being the inventor of the ERA patent. There are also a number of other registered protocols for studies investigating the effectiveness of the ERA test with the same author, which do not seem to ever have been published

[4] Serious heterogeneity unexplained by subgroup analysis: mean age of participants in both studies <35 years; there were no participants in either study with recurrent previous implantation failure

[5] 95% CI crosses 1 MID

[6] 95% CI crosses 2 MIDs

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

Table 6: Evidence profile for comparison between ERA-timed FET vs standard fresh ET

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ERT-timed FET**	**Standard fresh ET**	**Relative (95% CI)**	**Absolute**		
Live birth												

1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[4]	57/141 (40.4%)	64/145 (44.1%)	RR 0.92 (0.7 to 1.2)	35 fewer per 1000 (from 132 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL
Cumulative live birth at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	88/141 (62.4%)	85/145 (58.6%)	RR 1.06 (0.88 to 1.28)	35 more per 1000 (from 70 fewer to 164 more)	⊕OOO VERY LOW	CRITICAL
Clinical pregnancy at 5 weeks												
1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	76/141 (53.9%)	73/145 (50.3%)	RR 1.07 (0.86 to 1.34)	35 more per 1000 (from 70 fewer to 171 more)	⊕OOO VERY LOW	CRITICAL
Cumulative clinical pregnancy at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	132/141 (93.6%)	117/145 (80.7%)	RR 1.16 (1.06 to 1.27)	129 more per 1000 (from 48 more to 218 more)	⊕OOO VERY LOW	CRITICAL
Miscarriage (total pregnancy loss)												
1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	24/83 (28.9%)	16/84 (19%)	RR 1.52 (0.87 to 2.64)	99 more per 1000 (from 25 fewer to 312 more)	⊕OOO VERY LOW	IMPORTANT
Cumulative miscarriage (total pregnancy loss) at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	43/132 (32.6%)	28/117 (23.9%)	RR 1.36 (0.91 to 2.04)	86 more per 1000 (from 22 fewer to 249 more)	⊕OOO VERY LOW	IMPORTANT
Miscarriage (clinical pregnancy loss)												
1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	17/83 (20.5%)	5/84 (6%)	RR 3.44 (1.33 to 8.9)	145 more per 1000 (from 20 more to 470 more)	⊕⊕OO LOW	IMPORTANT
Cumulative miscarriage (clinical pregnancy loss) at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	24/132 (18.2%)	5/117 (4.3%)	RR 4.25 (1.68 to 10.79)	139 more per 1000 (from 29 more to 418 more)	⊕OOO VERY LOW	IMPORTANT
Miscarriage (biochemical pregnancy loss)												
1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	reporting bias[4]	7/83 (8.4%)	11/84 (13.1%)	RR 0.64 (0.26 to 1.58)	47 fewer per 1000 (from 97 fewer to 76 more)	⊕OOO VERY LOW	IMPORTANT
Cumulative miscarriage (biochemical pregnancy loss) at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	reporting bias[4]	19/132 (14.4%)	23/117 (19.7%)	RR 0.73 (0.42 to 1.27)	53 fewer per 1000 (from 114 fewer to 53 more)	⊕OOO VERY LOW	IMPORTANT
Ectopic pregnancy												
1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	reporting bias[4]	1/83 (1.2%)	1/84 (1.2%)	RR 1.01 (0.06 to 15.91)	0 more per 1000 (from 11 fewer to 177 more)	⊕OOO VERY LOW	IMPORTANT
Cumulative ectopic pregnancy at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	reporting bias[4]	1/132 (0.76%)	1/117 (0.85%)	RR 0.89 (0.06 to 14.01)	1 fewer per 1000 (from 8 fewer to 111 more)	⊕OOO VERY	IMPORTANT

											LOW	
Pregnancy loss												
1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	26/83 (31.3%)	18/84 (21.4%)	RR 1.46 (0.87 to 2.46)	99 more per 1000 (from 28 fewer to 313 more)	⊕OOO VERY LOW	IMPORTANT
Cumulative pregnancy loss at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	45/132 (34.1%)	30/117 (25.6%)	RR 1.33 (0.9 to 1.96)	85 more per 1000 (from 26 fewer to 246 more)	⊕OOO VERY LOW	IMPORTANT
Multiple gestation												
1 (Simon 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	8/57 (14%)	19/64 (29.7%)	RR 0.47 (0.22 to 1)	157 fewer per 1000 (from 232 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
Cumulative multiple gestation at 12 months												
1 (Simon 2020)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[4]	13/88 (14.8%)	27/85 (31.8%)	RR 0.47 (0.26 to 0.84)	168 fewer per 1000 (from 51 fewer to 235 fewer)	⊕OOO VERY LOW	IMPORTANT

CI: confidence intervals; ERA: Endometrial Receptivity Array; ET: embryo transfer; FET: frozen embryo transfer; LoNE: line of no effect; MID: minimally important difference; RoB: risk of bias; RR: risk ratio

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

[2] <150 events

[3] <300 events

[4] Publication bias suspected due to study with the most weight being industry funded by the company commercializing the ERA test and the author being the inventor of the ERA patent. There are also a number of other registered protocols for studies investigating the effectiveness of the ERA test with the same author, which do not seem to ever have been published

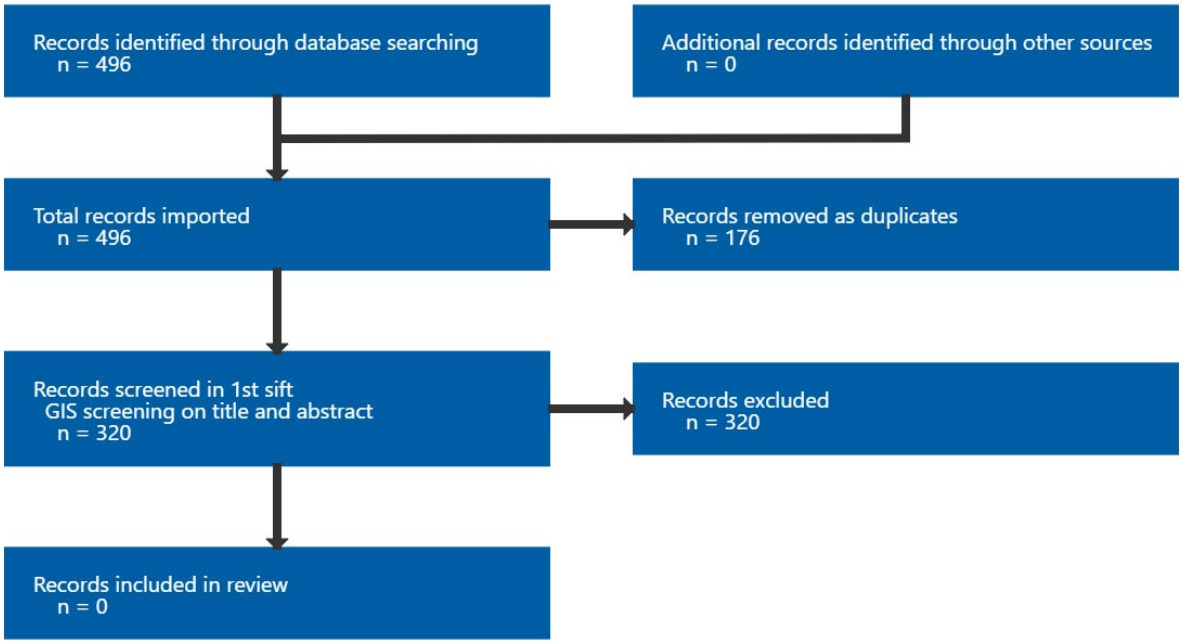
[5] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[6] 95% CI crosses 1 MID

[7] 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

No economic 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 tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

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 tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

Excluded effectiveness studies

Table 7: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Arian, Sara E, Hessami, Kamran, Khatibi, Ali et al. (2023) Endometrial receptivity array before frozen embryo transfer cycles: a systematic review and meta-analysis. Fertility and sterility 119(2): 229-238	- Systematic review - included studies checked for relevance
Bai, Xuechun, Zheng, Lianwen, Li, Dandan et al. (2021) Research progress of endometrial receptivity in patients with polycystic ovary syndrome: a systematic review. Reproductive biology and endocrinology : RB&E 19(1): 122	- Systematic review - included studies checked for relevance
Busnelli, A, Schirripa, I, Fedele, F et al. (2022) Obstetric and perinatal outcomes following programmed compared to natural frozen-thawed embryo transfer cycles: a systematic review and meta-analysis. Human reproduction (Oxford, England)	- Systematic review - included studies checked for relevance
Craciunas, Laurentiu, Gallos, Ioannis, Chu, Justin et al. (2019) Conventional and modern markers of endometrial receptivity: a systematic review and meta-analysis. Human reproduction update 25(2): 202-223	- Systematic review - included studies checked for relevance
Crha, I, Ventruba, P, Zakova, J et al. (2019) Uterine microbiome and endometrial receptivity. Ceska gynekologie 84(1): 49-54	- Article not available in English
Diaz-Gimeno, P., Sebastian-Leon, P., Sanchez-Reyes, J.M. et al. (2022) Identifying and optimizing human endometrial gene expression signatures for endometrial dating. Human Reproduction 37(2): 284-296	- Study design does not meet inclusion criteria *Non-comparative study*
Dieamant, Felipe C, Petersen, Claudia G, Mauri, Ana L et al. (2017) Fresh embryos versus freeze-all embryos - transfer strategies: Nuances of a meta-analysis. JBRA assisted reproduction 21(3): 260-272	- Systematic review - included studies checked for relevance
Haouzi, D, Entezami, F, Torre, A et al. (2021) Customized Frozen Embryo Transfer after Identification of the Receptivity Window with a	- Study design does not meet inclusion criteria *Non-randomised trial*

Study	Code [Reason]
Transcriptomic Approach Improves the Implantation and Live Birth Rates in Patients with Repeated Implantation Failure. Reproductive sciences (Thousand Oaks, Calif.) 28(1): 69-78	
He, Aihua, Zou, Yangyun, Wan, Cheng et al. (2021) The role of transcriptomic biomarkers of endometrial receptivity in personalized embryo transfer for patients with repeated implantation failure. Journal of translational medicine 19(1): 176	- Study design does not meet inclusion criteria *Non-randomised trial*
Jia, Y., Sha, Y., Qiu, Z. et al. (2022) Comparison of the Effectiveness of Endometrial Receptivity Analysis (ERA) to Guide Personalized Embryo Transfer with Conventional Frozen Embryo Transfer in 281 Chinese Women with Recurrent Implantation Failure. Medical Science Monitor 28: e935634	- Study design does not meet inclusion criteria *Non-randomised trial*
Lensen, Sarah, Shreeve, Norman, Barnhart, Kurt T et al. (2019) In vitro fertilization add-ons for the endometrium: it doesn't add-up. Fertility and sterility 112(6): 987-993	- Narrative review
Liu, Zhenteng, Liu, Xuemei, Wang, Meimei et al. (2022) The Clinical Efficacy of Personalized Embryo Transfer Guided by the Endometrial Receptivity Array/Analysis on IVF/ICSI Outcomes: A Systematic Review and Meta-Analysis. Frontiers in physiology 13: 841437	- Systematic review - included studies checked for relevance
Luo, Rong, Wang, Jiahui, Liu, Yi et al. (2023) Personalized versus standard frozen-thawed embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis. Journal of assisted reproduction and genetics	- Systematic review - included studies checked for relevance
Mackens, S., Santos-Ribeiro, S., van de Vijver, A. et al. (2017) Frozen embryo transfer: A review on the optimal endometrial preparation and timing. Human Reproduction 32(11): 2234-2242	- Narrative review
Maziotis, Evangelos, Kalampokas, Theodoros, Giannelou, Polina et al. (2022) Commercially Available Molecular Approaches to Evaluate Endometrial Receptivity: A Systematic Review and Critical Analysis of the Literature. Diagnostics (Basel, Switzerland) 12(11)	- Systematic review - included studies checked for relevance
Panchal Sonal, Y. and Nagori Chaitanya, B. (2010) Role of 3D and 3D power doppler to assess endometrial receptivity in IUI cycles. International Journal of Infertility and Fetal Medicine 1(1): 19-24	- Intervention/comparison does not meet inclusion criteria *Study did not explicitly compare embryo transfer guided by test for endometrial receptivity to embryo transfer without test for endometrial receptivity*
Qiong, Zhang, Jie, Hao, Yonggang, Wang et al. (2017) Clinical validation of pinopode as a marker	- Intervention/comparison does not meet inclusion

Study	Code [Reason]
of endometrial receptivity: a randomized controlled trial. Fertility and sterility 108(3): 513-517e2	criteria *Study investigates the effectiveness of pinopode assessment, which is not a genetic or microbiological analysis*
Rahmati, Mona and Macklon, Nick (2020) Testing the endometrium: is there enough evidence to justify clinical use?. Current opinion in obstetrics & gynecology 32(3): 185-190	- Narrative review
Ruiz-Alonso, Maria, Blesa, David, Diaz-Gimeno, Patricia et al. (2013) The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Fertility and sterility 100(3): 818-24	- Study design does not meet inclusion criteria *Non-randomised trial*
Zolfaroli, Irene, Monzo Miralles, Ana, Hidalgo-Mora, Juan Jose et al. (2023) Outcomes in patients undergoing embryo transfer: a systematic review and meta-analysis. Journal of assisted reproduction and genetics	- Systematic review - 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 tests for endometrial receptivity (including gene expression analysis and microbiological analysis) as a treatment add-on for people undergoing fertility treatment?

K.1.1 Research recommendation

Do treatments for identified endometrial abnormalities related to the microbiome or microbiological analysis (such as antibiotics to treat endometritis or microbiota transplantation) improve reproductive outcomes for people undergoing assisted reproduction?

K.1.2 Why this is important

If a microbiological endometrial abnormality is detected, it is important to know whether treatment can improve the success of embryo implantation in IVF.

K.1.3 Rationale for research recommendation

Table 8: Research recommendation rationale

Importance to 'patients' or the population	Failure of an embryo to implant following transfer into the uterus will lead to an unsuccessful cycle of IVF, so any treatment that can increase the chance of success will benefit people using IVF to treat a health-related fertility problem
Relevance to NICE guidance	No tests of endometrial receptivity are currently recommended in NICE guidelines, due to a lack of benefit or absence of evidence
Relevance to the NHS	Improving success rates for embryo implantation in IVF may lead to an increase in live births and reduce the need for repeat cycles of IVF which will save NHS resources
National priorities	High
Current evidence base	There is currently no RCT evidence for treatments based on results of these microbiological or microbiome tests for endometrial receptivity
Equality considerations	None identified.

Table 9: Research recommendation modified PICO table

Population	People undergoing microbiological or microbiome tests for endometrial receptivity as an add-on to treatment for a health-related fertility problem (including those with recurrent implantation failure)
Intervention	Treatment such as antibiotics or microbiota transplantation, following abnormal results of microbiological or microbiome tests for endometrial receptivity

Comparator	No treatment
Outcome	Live birth; clinical pregnancy; miscarriage; ectopic pregnancy; pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy); multiple gestation; implantation rate
Study design	Randomised controlled trial
Timeframe	Follow up to pregnancy loss or live birth

1