National Institute for Health and Care Excellence

Addendum to Clinical Guideline 156, Fertility problems: assessment and treatment

Clinical Guideline Addendum 156.1

Methods, evidence and recommendations

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Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

Contents

Clinical guidelines update

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's guidance executive.

Suitable topics for update are identified through the surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'. A further 3 topic experts were recruited to reflect the range of healthcare professionals and expertise in this field, and the range of views held.

In this document where 'the committee' is referred to, this means the entire committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the committee.

Details of the committee membership and the NICE team can be found in appendix A. A link to the committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

NICE published a guideline on the assessment and treatment of fertility problems in 2004, and this guideline was updated in 2013 (https://www.nice.org.uk/guidance/cg156/). As part of the 2013 update, recommendations on the use of intrauterine insemination were changed. Concerns were raised about the declarations of interest process that was followed when the recommendations about intrauterine insemination were discussed by the committee during the 2013 update. In order to address the concern raised the updates programme and committee were asked to reconsider the evidence for intrauterine insemination, with or without ovarian stimulation, compared with expectant management for people with unexplained infertility, mild endometriosis and mild male-factor infertility and whether the 2013 recommendations should be updated.

Some recommendations can be made with more certainty than others. The committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendations

1 For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse:

- do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF)
- advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[2016]**

1.3 Patient-centred care

This guideline offers best practice advice on the care of people with fertility problems.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.4 Methods

This update was developed based on the process and methods described in the Developing NICE Guidelines: the manual 2014.

2 Evidence review and recommendations

2.1 Introduction

Infertility is commonly defined as a problem conceiving for people of reproductive age, despite regular unprotected sexual intercourse. Around 1 in 7 couples in the UK are affected by infertility. Intrauterine insemination (IUI) is a procedure where sperm is processed in the laboratory to select the best quality sperm which are then placed inside a woman's uterus using a narrow tube. IUI can be 'stimulated' or 'unstimulated'. In stimulated IUI, insemination is co-ordinated with stimulation of the ovaries to produce at least 1 egg to attempt to improve the success of the procedure. The aim of this update is to review the evidence for the effectiveness of IUI compared with expectant management for people with unexplained infertility, mild endometriosis or 'mild' male factor infertility

2.2 Review question

What is the effectiveness of intrauterine insemination (IUI) compared with expectant management in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?

The original review question referred to the Clinical Guidelines Update Team did not highlight the comparison in the evidence review. The review question has been reworded slightly to include 'compared with expectant management' to clarify the comparison of this evidence review.

2.3 Clinical evidence review

2.3.1 Methods and results

A systematic review of the literature was conducted, as specified in the review protocol in Appendix C. The protocol was developed in consultation with the topic expert members and then reviewed by the core Committee members before the review was carried out. All outcomes included in the review were considered important. These outcomes are: live full-term singleton birth; clinical pregnancy rate; adverse pregnancy outcome; multiple births; ovarian hyperstimulation syndrome; fetal abnormalities, patient outcomes; anxiety and/or depression. Where live full-term singleton birth was not reported by a study, the outcome live birth or live singleton birth were used as proxy measures and the quality of evidence was downgraded for indirectness. This is because the outcome live births may incorporate preterm births and multiple births, both of which are negative outcomes. Subsequently, the live singleton births may incorporate preterm births.

A systematic search (see appendix D) identified 625 articles from the date of last search (30th November 2011). The titles and abstracts were screened and 12 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 12 were excluded as they did not meet the criteria and 7 articles were included from the original guideline. Of these, one article was a secondary publication of other included studies, leaving 6 included studies in total.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

For a summary of included studies see Table 1 (for the full evidence tables and full GRADE profiles please see appendices G and H). Evidence was available for the following comparisons included in the evidence review:

- IUI without ovarian stimulation versus expectant management
- IUI with ovarian stimulation versus expectant management
- IUI with ovarian stimulation versus IUI without ovarian stimulation

These comparisons were included, in accordance with the review protocol, to examine the effect of IUI with or without ovarian stimulation compared to expectant management or different forms of IUI. When more than one study assessed an outcome for a given comparison, data were combined using pair-wise meta-analyses. The Mantel-Haenszel and inverse variance methods were used for dichotomous and continuous outcomes, respectively. A fixed effects model was chosen because no difference in effect estimates were seen when tested by using a random effects model. Additionally, only one meta-analysis was conducted on the outcome (pregnancy rate - multiple pregnancies) for one comparison (IUI with stimulation versus IUI without stimulation) and this showed a very minor change (of 0.04) in pooled risk ratio when using random effects. The I^2 statistic was calculated to assess heterogeneity. Forest plots showing the outcome of these meta-analyses are shown in appendix I.

Assessment of subgroup effects was possible for one comparison (IUI versus expectant management) for the outcome of live birth. Evidence was available for the subgroups: unexplained infertility, mild male factor and mild endometriosis. Evidence was not available to assess subgroup effects in all other outcomes in the included comparisons.

The quality of evidence for each outcome for each comparison was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (for full GRADE profiles, see appendix H). All included studies were randomised controlled trials. Risk of bias was assessed based on blinding and allocation concealment and possible attrition bias (for example, clear differences in drop-out rates). Indirectness was assessed on the applicability of the population, treatment and outcome to the review protocol. Inconsistency was assessed on heterogeneity levels (I^2 result) of meta-analysis. Heterogeneity was considered serious if $I^2 \geq 50\%$ and very serious if $I^2 \geq 70\%$.

Published minimally important differences were sought for all outcomes via an internet search and through reference to the original NICE guideline on fertility, but none were found. The GRADE default minimally important differences (MIDs) were used (0.75 and 1.25 for dichotomous outcomes, and for continuous outcomes, either 50% of 95%CI around point estimate of control group at baseline for mean difference and -0.5 and 0.5 standardised mean differences). Imprecision was assessed using the MIDs as thresholds for 95% confidence intervals (CIs) of effect estimates (relative risk (RR) for dichotomous outcomes and mean differences for continuous outcomes). Imprecision was considered serious and downgraded by one level if 95% CIs crossed one MID or very serious and downgraded by two levels if 95% CIs crossed both MIDs. Other factors such as publication bias were also considered, but none gave rise to serious uncertainty.

To determine clinical effectiveness, where 95% CIs of an effect estimate crosses an MID, the effect of the intervention or control is uncertain. This uncertainty is captured in the evidence statements when the word ‘may’ is used (for example, may be higher). Where 95% CIs of an effect estimate crosses the line of no effect there may be no difference between intervention and comparison and this is highlighted in the evidence statement.

Table 1: Summary of included studies

Study id	Population	Intervention & comparator	Location	Outcomes reported
IUI without ovarian stimulation vs expectant management				
Bhattacharya 2008	Couples with unexplained infertility	IUI without ovarian stimulation vs expectant management	Scotland	Live births (all, unexplained infertility, mild male factor, mild endometriosis, mild endometriosis and mile male factor) Pregnancy rate Pregnancy related adverse events Patient related adverse events Patient satisfaction Anxiety Depression
IUI with ovarian stimulation vs expectant management				
Steures 2006	Couples with unexplained infertility	IUI with ovarian stimulation vs expectant management	The Netherlands	Live birth Pregnancy rate (6 month treatment duration) Pregnancy related adverse events (6 month treatment duration)
Tummon 1997	Couples with infertility associated with mild or moderate endometriosis	IUI with ovarian stimulation vs expectant management	Canada	Live singleton birth and live births OHSS
IUI with ovarian stimulation vs IUI without ovarian stimulation				
Cohlen 1998	Couples with male-factor infertility	IUI with ovarian stimulation vs IUI without ovarian stimulation	The Netherlands	Pregnancy rate
Goverde 2005 (secondary publication of Goverde 2000)	Couples with unexplained infertility or mild to moderate male-factor infertility	IUI with ovarian stimulation vs IUI without ovarian stimulation	The Netherlands	Live births Pregnancy rate
Guzick 1999	Couples with unexplained infertility or male-factor infertility	IUI with ovarian stimulation vs IUI without ovarian stimulation	USA	Live births Pregnancy rate Pregnancy related adverse events

IUI: intrauterine insemination, OHSS: ovarian hyperstimulation syndrome

2.4 Health economic evidence review

2.4.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist undertook a systematic review of the published economic literature.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to intrauterine insemination (IUI) compared with expectant management in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 16.12.2015 (NHS EED and HTA) and 17.12.2015 (Medline and Embase). The health economic search strategies are detailed in appendix J.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual 2014*.
- Extracted key information about the studies' methods and results into full economic evidence tables (appendix M).
- Generated summaries of the evidence in economic evidence profiles.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix L).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H* of *Developing NICE Guidelines: the manual 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty.

Table 2 explains the information contained in the economic evidence profile.

Table 2: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental	The difference between the mean health effect associated with the intervention

Item	Description
effect	and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance with the NICE reference case.
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

2.4.2 Results of the economic literature review

The search returned 142 articles. 136 of these were excluded based on title and abstract. Full papers were obtained for 6 articles. 5 full text articles were excluded. Only one study from the published literature was included.

The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix K. Appendix L contains a list of excluded studies and the reason for their exclusion.

Table 4 contains the economic evidence profile for the review question summarising the results of the study included in the systematic review. Full economic evidence tables are contained in appendix M.

The single included study (Wordsworth et al. 2011) was also included in the existing NICE guideline on fertility and was a within-trial economic evaluation of the SUIT trial. It investigated the cost effectiveness of expectant management in comparison to intrauterine insemination (and also versus clomifene citrate) in people with unexplained infertility. The ICER for IUI versus EM was £5604 (-12 204 to £2227) per additional live birth, with CC always being dominated. The authors concluded that, these results suggest that IUI could only be considered cost-effective if EM were not an option, although this was applying a

willing to pay threshold of £5,000 per additional live birth. This study was partially applicable with very serious limitations, which included no use of QALYs, a short time horizon, statistically insignificant effect size on the primary outcome and use of potentially inappropriate costs.

Table 3: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	Effect	ICER	
Wordsworth et al. 2011 Expectant management (EM) vs. unstimulated intrauterine insemination (IUI) vs. clomifene citrate (CC) United Kingdom	Partially applicable [(a)]	Very serious limitations [(b)]	Within-trial analysis	£319.39	0.06	£5,604 per additional live birth	The one-way sensitivity analysis demonstrated that, the ICER for IUI versus EM treatment was highest when staff costs for IUI were increased by 50% at £6618. If the cost-effectiveness ceiling ratio is £30 000 per an additional live birth, EM has approximately a 15% probability of being the most cost-effective intervention, while IUI has approximately an 80% chance. But if decision makers are willing to pay £5000 per an additional live birth, it is EM which has an 80% probability of being the most cost-effective intervention, while IUI has approximately a 30% chance (read off graph). Probability of finding a particular intervention the most cost-effective is driven by small differences in effectiveness, while differences in costs become less important if there is a greater willingness to pay for a given increase in effectiveness.

Acronyms

1 *EM: Expectant Management; IUI: Intrauterine Insemination; QALY: quality-adjusted life year*

2 *(a) Scottish study from an NHS perspective. QALYs not used as an outcome. May not be sufficiently recent to reflect current practice.*

3 *(b) Short time horizon. QALYs not included as outcomes. Estimates of costs and resource use may not appropriately reflect all relevant evidence sources.*

2.5 Evidence statements

2.5.1 Clinical evidence statement

2.5.1.1 IUI without ovarian stimulation versus expectant management

One RCT (N = 386) reported evidence on IUI without ovarian stimulation versus expectant management:

- Very low quality evidence showed there may be no difference in live births for all participants and for those with unexplained fertility, with inconclusive evidence for mild male factor and mild endometriosis.
- Very low quality evidence showed there may be no difference in the number of clinical pregnancies and there was inconclusive evidence for the number of multiple pregnancies.
- Very low quality evidence for pregnancy-related adverse events was inconclusive, but IUI without ovarian stimulation may be associated with a lower rate of miscarriage.
- Very low quality evidence was found for patient related adverse events, with inconclusive evidence for treatment related hospital admissions, nausea, hot flushes and bloating, yet low quality evidence showed there may be no difference in abdominal pain and vaginal bleeding.
- Very low quality evidence showed there may be lower total adverse events with expectant management.
- Very low quality evidence showed that patient satisfaction was higher with IUI without ovarian stimulation.
- Low quality evidence showed anxiety was lower with expectant management and very low quality evidence was inconclusive for depression.
- No evidence was found for multiple births and ovarian hyperstimulation syndrome.

2.5.1.2 IUI with ovarian stimulation versus expectant management

Two studies with a total of N = 370 couples with either unexplained infertility or mild endometriosis were included for IUI with ovarian stimulation versus expectant management:

- Low quality evidence from 1 study showed there may be no difference in live singleton births in IUI with stimulation compared to expectant management in women with mild endometriosis.
- Very low quality evidence from 1 study showed live births determined, in the study by interview may be higher in IUI with stimulation in women with mild endometriosis.
- Very low quality evidence from 1 study was inconclusive for live births in couples with unexplained infertility.
- Very low quality evidence from 1 study was inconclusive for pregnancy rate with 6 months treatment in couples with unexplained infertility.
- Moderate quality evidence from 1 study was inconclusive for ovarian hyperstimulation syndrome in women with mild endometriosis.
- Very low quality evidence from 1 study showed there may be no difference in miscarriage at 6 months in couples with unexplained infertility.
- No evidence was found for fetal abnormalities, patient outcomes, anxiety and/or depression.

2.5.1.3 IUI with ovarian stimulation versus IUI without ovarian stimulation

Two studies with a total of N = 710 couples with unexplained infertility and mild to moderate subfertility were included for IUI with ovarian stimulation versus IUI without ovarian stimulation:

- Very low quality evidence from 1 RCT was inconclusive for live singleton birth.
- Very low quality evidence from 2 studies combined in a meta-analysis showed that live births may be higher in IUI with stimulation with up to or including 4 treatment cycles in couples with unexplained infertility and male subfertility.
- Very low quality evidence found from 1 study was inconclusive for pregnancy rates per treatment cycle. Very low quality evidence from another study was inconclusive for singleton pregnancy and found there may be no difference in ongoing pregnancy with 4 cycles of IUI with stimulation.
- Moderate quality evidence from 1 study showed higher pregnancy rates per couples with infertility with up to 4 cycles of IUI with stimulation.
- Moderate quality evidence from 2 studies combined in a meta-analysis showed IUI without stimulation with up to and including 4 cycles was associated with fewer multiple pregnancies in couples with unexplained infertility and male subfertility.
- Moderate quality evidence from 1 study showed total adverse events was lower with up to 4 cycles of IUI without stimulation in couples with male subfertility.
- Low quality evidence showed preterm birth may be lower with IUI without stimulation and very low quality evidence was inconclusive for stillbirths, ectopic pregnancies and induced abortions in couples with male subfertility.
- Moderate quality evidence from 1 study found IUI without stimulation with up to 4 cycles was associated with a lower rate of miscarriage in couples with male subfertility.
- No evidence was found for multiple births, ovarian hyperstimulation syndrome, patient outcomes and anxiety and/or depression.

2.5.2 Health economic evidence statements

One within trial economic evaluation conducted from a UK NHS perspective concluded that IUI would only be considered cost effective if expectant management was not an option, although this was applying a willingness-to-pay threshold of £5,000 per additional live birth. A threshold analysis concluded that the live birth rate of IUI would have to rise from 22% to 27% (compared with 17% on expectant management) to become cost effective. This economic evaluation was assessed as partially applicable with serious limitations. Limitations included no use of QALYs, short time horizon, statistically insignificant effect size on the primary outcome and use of potentially inappropriate costs.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The committee selected live full-term singleton birth as a critical outcome for decision making as this allows clinicians to inform women and couples of their likelihood of safely having a healthy baby. The committee selected clinical pregnancy rate as a critical outcome as this reflects the success of the procedure and some studies may not report live singleton birth. However, it was noted that a limitation could be that it is normal practice for women who become pregnant to be discharged from the fertility clinic to routine antenatal care. Consequently, data on the outcome of pregnancies may therefore be incomplete.

	Committee discussions
	The committee selected multiple births as a critical outcome as this is the main risk of fertility treatments for a mother and the babies. Multiple birth is linked to preterm birth, low birth weight and neonatal mortality in the baby and pre-eclampsia in the mother. The committee considered adverse events as a critical outcome as this is the main reason treatment is discontinued or reconsidered. Such adverse events include preterm birth, stillbirth and miscarriage. The committee considered ovarian hyperstimulation syndrome (OHSS), foetal abnormalities, patient-related outcomes including clinical symptoms and quality of life and anxiety and/or depression as important outcomes for decision making.
Quality of evidence	The quality of the evidence ranged from moderate to very low. The main reason for downgrading the quality of the evidence was for a lack of blinding and serious or very serious imprecision. The committee noted that very low quality evidence available for the comparison of IUI without ovarian stimulation versus expectant management. Two of the included studies used intention to treat analysis, though a proportion of participants randomised to expectant management received IUI during the trial period. In these cases, indirectness was downgraded due to serious indirectness. The committee discussed that it is not possible to blind participants or clinicians to treatment with intrauterine insemination (with or without stimulation) versus expectant management. This lack of blinding in the included studies may not introduce bias for objective measures, such as live singleton birth and clinical pregnancy rate. In contrast, blinding may be possible in trials comparing IUI with stimulation versus IUI without stimulation. However, the included studies for this comparison did not state if participants or clinicians were blinded to treatment, The Committee agreed that it is appropriate to apply standard GRADE criteria and downgrade these outcomes as it is unclear if bias was introduced due to lack of blinding.
Trade-off between benefits and harms	The committee acknowledged the challenges and stresses that are experienced by people when undergoing fertility treatment, especially those who are on the waiting list for treatment and those who have undergone, sometimes multiple courses of, unsuccessful treatments. The committee noted that the majority of evidence for IUI without stimulation versus expectant management was inconclusive yet there was evidence to suggest that patient satisfaction is greater in the IUI group. However, a greater number of participants in the IUI group had anxiety than in the expectant management group. This possibly highlights the stresses on the woman while undergoing treatment, even if women are satisfied with process, and possibly outcome, of treatment. The committee raised concerns that the study included in this comparison only used urine testing to determine ovulation, while many clinics use ultrasound and/or blood tests. Additionally, it was noted that this study has a small sample size which may not have statistical power to determine clinical benefit or harm. The committee noted that evidence for IUI with ovarian stimulation versus expectant management was inconclusive. Additionally, concerns were raised regarding the population included in one trial (Steures 2006) as 20% of couples in the expectant management group receive IUI prior to the trial completion. These couples were reported in one outcome (pregnancy rate) and it was agreed that the quality of evidence will be downgraded on the basis of indirectness of treatment as it was not possible to dis-aggregate the data. This is because establishing a true effect estimate of IUI with

	Committee discussions
	stimulation compared to expectant management would not be possible. The committee noted that evidence for IUI with ovarian stimulation versus IUI without ovarian stimulation was generally inconclusive. However, moderate quality evidence found that miscarriages were higher in the IUI with stimulation group. The committee noted that this is consistent with their clinical experience and agreed that based on their knowledge and experience, IUI with stimulation is associated with higher risk of miscarriage, likely owing to the higher risk of multiple pregnancy. The committee agreed that the evidence is inconclusive and does not favour any one intervention. Additionally, there was a lack of or no evidence on some subgroups specified in the review protocol, specifically: mild male factor infertility and age. For this reason, the committee agreed that there was insufficient new evidence to justify a change to the recommendations. The committee also discussed the current "do not routinely offer" IUI recommendation (1.9.1.3) and noted that the current wording could be considered strong in light of the weak evidence base. However, the committee also acknowledged that the current wording of the recommendation encouraged consideration of IUI as a treatment option in some circumstances, for example when people have social, cultural or religious objections to IVF. The committee agreed that a recommendation with a 'do not routinely offer' wording provides some flexibility, whereas a 'do not offer' recommendation provide definitive guidance against the use of an intervention. The committee also discussed changing 'IVF' in recommendation 1.9.1.3 to 'assisted conception'. However, evidence in relation to all assisted conception methods were not reviewed in this guideline update to allow this change. The committee agreed that the evidence did not justify a change to the recommendations.
Trade-off between net health benefits and resource use	One published economic evaluation met the inclusion criteria. This study was also identified in the previous guideline and concluded that IUI without ovarian stimulation could only be considered cost effective if expectant management was not an option, although this was using a willingness-to-pay threshold of £5,000 per additional live birth. The paper was assessed as partially applicable with very serious limitations, which included no use of QALYs, a short time horizon, statistically insignificant effect size on the primary outcome and use of potentially inappropriate costs. The committee considered this evidence and decided that the original recommendations should stand. The committee noted that no evidence was identified in the clinical review that would lead to a change in recommendations so no new economic analysis was prioritised. The committee noted that there would be no resource impact as no recommendations have been added or altered.

	Committee discussions
Other considerations	The committee noted that the Human Fertilisation & Embryology Authority (HFEA) database contains success rates for IUI and discussed the applicability of this data. The committee were informed by topic experts that this data could not be aggregated by cause of infertility and as such could not inform the committee's deliberations. The committee noted that all the trials included are over 10 years old and clinical practice has evolved since the publication of these trials. The committee reviewed the research recommendations (number 22 and 23) made in the 2013 guideline update and noted that up to date research to examine the effectiveness of IUI (with and without stimulation) compared to expectant management in couples with endometriosis and mild male factor infertility had been recommended. The committee felt that the research recommendations outlined in the 2013 guideline update covered the research that they would like to recommend and therefore did not make any new research recommendations. However, they discussed possible reasons for lack of more up to date research in this area including increased research interest into other methods of fertility treatments, difficulty in recruitment within these specific populations and the difficulties in quantifying quality of life over multiple cycles of treatment. The committee noted that the mean ages of the women in the trials included were in the low thirties, and there is an absence of evidence for later age groups which the topic experts commonly see in clinical practice, especially among those who have had two years of expectant management so it was difficult to be able to generalise these findings to clinical practice. Finally, the committee noted the limitations of considering an update of a section of a guideline without considering the broader aspects of the care pathway. It was noted that there is recent evidence to compare IUI with in-vitro fertilisation (IVF) identified by the NICE surveillance review and the committee were informed that this will be considered in a future update of this guideline. The committee discussed concerns regarding the funding available for IUI based on the current recommendations and the potential for IUI units closing before this update is completed. <u>Equality issues</u> The committee noted that access to fertility services by people can be limited and can vary by geographical location. Additionally, it was noted that geographical isolation, for example those living in rural areas, may be a barrier to receiving fertility treatment as people may not be able or willing to travel long distances for fertility clinics on a regular basis The committee noted that there are geographical variances in service provision and availability of treatments in different commissioning centres. The committee raised that single women may have more limited access to fertility services compared to couples as fertility services may be more willing to offer fertility treatment to couples. The committee also noted that some commissioning centres do not recognise same-sex couples for fertility treatment. Furthermore, same sex female couples may find it more difficult in practice to access treatment because they cannot demonstrate having 'tried' to get pregnant for a certain amount of time, unless they have already paid for IUI privately. However, the committee felt that provision of fertility treatment to same-sex couples was adequately covered in recommendation 1.9.1.1. This recommendation covers that unstimulated IUI may be considered in the following groups as an alternative to vaginal sexual intercourse: people who are unable to, or would find it very difficult to, have vaginal intercourse, people with conditions that require specific consideration in relation to methods of conception and people in same-sex relationships.

	Committee discussions
	The committee noted that, from their experience, there are different types and levels of information regarding fertility treatment, including IUI, available to women and couples across the UK. The committee noted that income and ability to pay for treatment may provide a limitation for women and couples who seek self-funded treatment when NHS treatment is not available at the level that NICE recommends.

2.7 Recommendations

1 For people with unexplained infertility, mild endometriosis or mild male factor infertility, who are having regular unprotected sexual intercourse:

- do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF)
- advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[2016]**

3 References

Clinical review

Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulatedintrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337,pp.a716, -, 2008

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Tummon,I.S., Asher,L.J., Martin,J.S., Tulandi,T., Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis, Fertility and Sterility, 68, 8-12, 1997

Health economic review

Wordsworth,S., Buchanan,J., Mollison,J., Harrild,K., Robertson,L., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Bhattacharya,S., Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective?, Human Reproduction 2011 Feb;26(2):369-75

4 Glossary

Please refer to the NICE glossary.

Clinical pregnancy: a pregnancy diagnosed by ultrasonographic visualisation of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy. Note: Multiple gestational sacs are counted as one clinical pregnancy. (Zegers-Hochschild et al., 2009)

Clinical pregnancy rate: the number of clinical pregnancies expressed per 100 initiated cycles, aspiration cycles or embryo transfer cycles. Note: When clinical pregnancy rates are given, the denominator (initiated, aspirated or embryo transfer cycles) must be specified. (ZegersHochschild et al., 2009)

Expectant management: this is a formal approach that encourages conception through unprotected vaginal intercourse. It involves supportively offering an individual and/or couple information and advice about the regularity and timing of intercourse and any lifestyle changes which might improve their chances of conceiving. This approach does not involve any active clinical or therapeutic interventions.

Intrauterine insemination: clinical delivery of sperm into the uterine cavity

Mild male factor infertility: The term ‘mild’ male factor infertility is used extensively in practice and in the literature. However, no formally recognised definition of what this means is currently available. Therefore, where the term ‘mild’ male factor infertility is applied in this guideline, it is defined as meaning: two or more semen analyses that have one or more variables which fall below the 5th centile as defined by WHO, 2010, and where the effect on the chance of pregnancy occurring naturally through vaginal intercourse within a period of 24 months would then be similar to people with unexplained infertility or mild endometriosis.

Appendices

Appendix A: Standing Committee members and NICE teams

A.1 Core members

Name	Role
Catherine Briggs (until February 2016)	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies (until February 2016)	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Professor, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Kath Nuttall (until November 2015)	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset
Philippa Williams	Lay Member
Sophie Wilne (Chair)	Paediatric Oncologist, Nottingham Children's Hospital

A.2 Topic expert Committee members

Name	Role
Kate Brian	Lay member
Geraldine Hartshorne	Head of Clinical Faculty, Warwick Medical School/University Hospitals Coventry and Warwickshire NHS Trust
Kanna Jayaprakasan	Consultant Gynaecologist/ Fertility Unit Lead, Royal Derby Hospital, Derby/ University of Nottingham
Kay Kuntawala	Senior Fertility Sister, Centre for Reproductive Medicine St Bartholomew's Hospital
Stuart Lavery	Consultant Gynaecologist/Director IVF, Hammersmith Hospital
Jonathan Lord	Consultant in Obstetrics & Gynaecology, Royal Cornwall Hospital
Anthony Rutherford	Consultant in Reproductive Medicine & Gynaecological Surgery, Leeds Surgery
Jan Wake	GP sexual and reproductive health, DeMontfort Surgery, Leicester

A.3 NICE project team

Name	Role

Name	Role
Mark Baker	Clinical Advisor
Steven Barnes	Technical Lead
Christine Carson	Guideline Lead
Jessica Fielding	Public Involvement Advisor
Bhash Naidoo	Technical Lead (Health Economics)
Ben Doak	Guideline Commissioning Manager
Trudie Willingham	Guideline Co-ordinator

A.4 Clinical guidelines update team

Name	Role
Philip Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Anna Zaremba / Ross Maconachie	Health Economist
Sarah Glover	Information Specialist
Kathryn Hopkins / Omnia Abdulrazeg	Technical Analyst
Nick Lowe/Emma Carter	Administrator
Hugh McGuire	Technical Advisor
Susannah Moon	Programme Manager
Ian Pye	Assistant Project Manager
Lorraine Taylor	Associate Director

Appendix B: Declarations of interest

Declarations of interest for Core committee members and Topic experts can be found here

Appendix C: Review protocol

Review Protocol	
Components	**Details**
Review question	What is the effectiveness of intrauterine insemination (IUI) compared with expectant management in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?
Background/objectives	To determine the effectiveness of IUI with and without ovarian stimulation, compared with expectant management in couples with unexplained infertility, mild male factor or endometriosis
Types of study to be included	Randomised controlled trials, systematic reviews of randomised controlled trials
Language	English
Status	Full text articles
Population	People with: Unexplained infertility: defined as infertility when standard investigations, including semen analysis, tubal patency tests and assessment of ovulation, fail to identify any abnormalities or a specific diagnosis. Studies that do not use this definition but describe the population as 'unexplained infertility' will also be included, and the applicability of the evidence discussed with the Committee. Mild male factor infertility: defined as two or more semen analyses that have one or more variables which fall below the 5th centile as defined by WHO, 2010, and where the effect on the chance of pregnancy occurring naturally through vaginal intercourse within a period of 24 months would then be similar to people with unexplained infertility or mild endometriosis. Studies that do not use this definition but describe the population as 'mild male factor' infertility will also be included, and the applicability of the evidence discussed with the Committee. Mild endometriosis: defined according to the American fertility society criteria, or as specified by study authors.
Intervention	Unstimulated single* IUI (no ovulation induction agents used) Stimulated single* IUI (ovulation induction agents used) *where single means that 1 insemination is carried out per cycle.
Comparator	Either intervention listed above Expectant management
Outcomes	Live full-term singleton birth Clinical pregnancy rate Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery)

Review Protocol	
Components	**Details**
	Multiple births Ovarian hyperstimulation syndrome Fetal abnormalities Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life Anxiety and/or depression Cumulative outcome measures over a course of treatment will be preferred to outcomes reported per cycle.
Any other information or criteria for inclusion/exclusion	Non-human studies will be excluded The first phase only of cross over trials will be included. Selection of papers: i) Selection based on titles and abstracts Full double-sifting of titles and abstracts will not be conducted due to the straightforward nature of the review question (intervention question with clearly defined interventions and comparators). ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). Other mechanisms will be in place for quality assurance: Internal quality assurance by CGUT technical adviser on the reasons for inclusion and exclusion. As an additional check the Committee will be sent the list of included and excluded studies prior to the committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and (in the case of topic expert members) whether there are any relevant studies they have known of which have not been identified by the searches.
Analysis of subgroups or subsets	Unexplained infertility, mild endometriosis, mild male factor infertility. Type of ovarian stimulation when the intervention is stimulated IUI. Age.
Data extraction and quality assessment	Key features of included studies and reported outcomes will be extracted into evidence tables. The quality of evidence for each outcome will be assessed using the approach for intervention questions outlined by the GRADE working group. Reliability of quality assessment: A full double-scoring quality assessment will not be conducted due to the nature of the review question (as mentioned above) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: Internal quality assurance by CGUT technical adviser on the quality assessment that is being conducted. As an additional check, the Committee will be sent the evidence synthesis prior to the committee

Review Protocol	
Components	**Details**
	meeting and the Committee will be requested to comment on the quality assessment (GRADE profiles), which will serve as another quality assurance function.
Strategy for data synthesis	Data for each outcome from different studies will be synthesised using pairwise meta-analysis where possible. Where synthesis by meta-analysis is not possible, data will be presented for individual studies.
Searches	Sources to be searched Clinical searches - Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. Economic searches - Medline, Medline in Process, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques None identified Limits Studies reported in English Study design randomised controlled trial and systematic review filters will be applied Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results Papers indexed since 30/11/2011 (last search date for 2013 review)

Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in **Error! Reference source not found.**.

Table 4: Clinical search summary

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	16/12/2015	11 of 12 November 2015	A 214 B 33
Cochrane Database of Systematic Reviews (CDSR)	16/12/2015	12 of 12 December 2015	A 13 B 1
Database of Abstracts of Reviews of Effect (DARE)	16/12/2015	2 of 4 April 2015	A 5 B 0
Embase (Ovid)	16/12/2015	1974 to 2015 December 15	A 250 B 92
MEDLINE (Ovid)	16/12/2015	1946 to November wk 3 2015 (NB Ovid reload period)	A 169 B 89
MEDLINE In-Process (Ovid)	16/12/2015	Dec 10 2015	A 32 B 3
PubMed			28
Health Technology Assessment (HTA Database)	16/12/2015	4 of 4 October 2015	A 0 B 1

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The results were divided into two sets to enable separate analysis of the terms added to the original strategy; set A represents the results at line 53 and set B at line 58. The aim of the search was to identify evidence for the clinical question being asked.

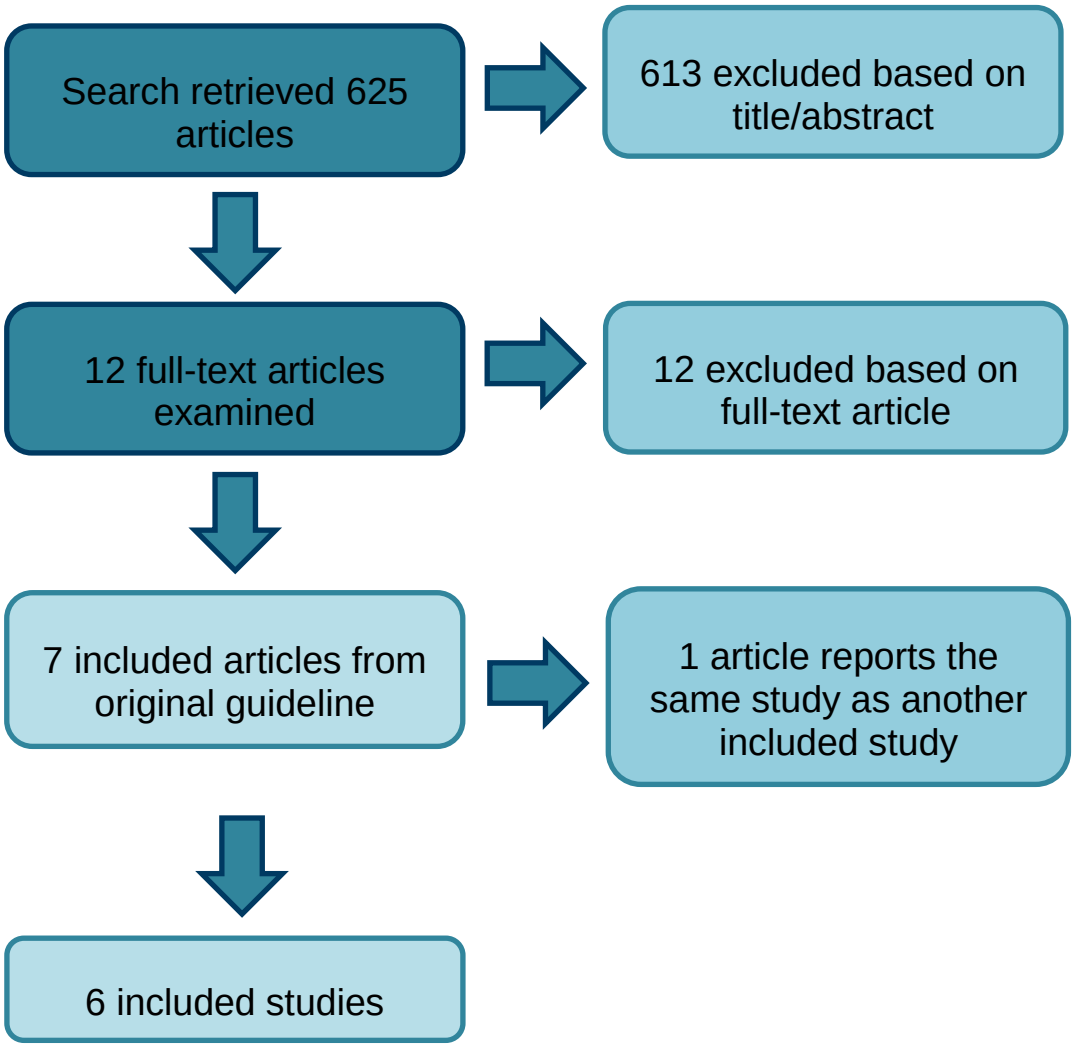
The Pubmed translation consisted of an abbreviated strategy run at the end of the process designed to capture references that had not yet appeared in the Medline in Process database. Randomised Controlled Trial and Systematic Review filters were used to identify the study designs specified in the Review Protocol.

Table 5: Clinical search terms (Medline/MIP)

Line number/Search term/Number retrieved
1 (fertil* or steril* or infertil* or subfertil* or sub-fertil* or fecund* or subfecund* or sub-fecund* or assist* reproduc*).tw.
2 exp Infertility/
3 Infertility, Female/
4 Infertility, Male/ 5 Anovulation/
6 anovulat*.tw.
7 (oligo-ovulation or "oligo ovulation" or oligoovulat*).tw.
8 Endometriosis/

Line number/Search term/Number retrieved
9 endometrio*.tw.
10 or/1-9
11 exp Insemination, Artificial/
12 ((artificial* or homologous or heterologous) adj4 inseminat*).tw.
13 (iui or siui).tw.
14 ((intrauterine or intra-uterine) adj inseminat*).tw.
15 or/11-14
16 10 and 15
17 Randomized Controlled Trial.pt.
18 Controlled Clinical Trial.pt.
19 Clinical Trial.pt.
20 exp Clinical Trials as Topic/
21 Placebos/
22 Random Allocation/
23 Double-Blind Method/
24 Single-Blind Method/
25 Cross-Over Studies/
26 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
27 (random$ adj3 allocat$).tw.
28 placebo$.tw.
29 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (133529)
30 (crossover$ or (cross adj over$)).tw.
31 or/17-30
32 animals/ not humans/
33 31 not 32
34 Meta-Analysis.pt.
35 Meta-Analysis as Topic/
36 Review.pt.
37 exp Review Literature as Topic/
38 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
39 (review$ or overview$).ti.
40 (systematic$ adj5 (review$ or overview$)).tw.
41 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
42 ((studies or trial$) adj2 (review$ or overview$)).tw.
43 (integrat$ adj3 (research or review$ or literature)).tw.
44 (pool$ adj2 (analy$ or data)).tw.
45 (handsearch$ or (hand adj3 search$)).tw.
46 (manual$ adj3 search$).tw.
47 or/34-46
48 animals/ not humans/
49 47 not 48
50 33 or 49
51 16 and 50
52 limit 51 to english language
53 limit 52 to ed=20111130-20151216
54 8 or 9
55 15 and 54
56 50 and 55
57 limit 56 to english language
58 57 not 53

Appendix E: Review flowchart



Appendix F:Excluded studies

Study	Reason for Exclusion
Barnes,A., Riche,D., Mena,L., Sison,T., Barry,L., Reddy,R., Shwayder,J., Parry,J.P., 20140929, Efficacy and safety of intrauterine insemination and assisted reproductive technology in populations serodiscordant for human immunodeficiency virus: a systematic review and meta-analysis. [Review], Fertility & Sterility, 102, 424-434, 2014	Incorrect study design: systematic review of observational studies
Crosignani,P.G., Walters,D.E., 19941215, Clinical pregnancy and male subfertility; the ESHRE multicentre trial on the treatment of male subfertility. European Society of Human Reproduction and Embryology, Human Reproduction., 9, 1112-1118, 1994	Incorrect comparison (group not received IUI received ovarian stimulation).
Custers,I.M., van Rumste,M.M., van der Steeg,J.W., van,Wely M., Hompes,P.G., Bossuyt,P., Broekmans,F.J., Renckens,C.N., Eijkemans,M.J., van Dessel,T.J., van,der,V, Mol,B.W., Steures,P., CECERM, 20120518, Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment, Human Reproduction., 27, 444-450, 2012	Follow-up study of Steures 2006 (included). During follow-up period, some women (42 in expectant management group and 44 in IUI group) received IVF.
Dickey,R.P., Olar,T.T., Clomiphene citrate-induced intrauterine insemination cycles, Assisted Reproduction Reviews., 3, 108-120, 1993	Incorrect study type: narrative review.
Dodson,W.C., Is superovulation and intrauterine insemination really an alternative to assisted reproductive technology?, Seminars in Reproductive Endocrinology., 13, 85-89, 1995	Incorrect study type: narrative review.
Gautam,A., Does the addition of gonadotropin-releasing hormone analogs improve the pregnancy rates in intrauterine insemination?, Journal of Obstetrics and Gynecology of India, 61, 261-264, 2011	Incorrect study type: editorial/commentary
Guzick,D.S., 19970930, Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis, Journal of Women's Health, 6, 489-490, 1997	Incorrect study design: commentary
Houwen,L.E.E., Schreurs,A.M.F., Lambalk,C.B., Schats,R., Hompes,P.G.A., Mijatovic,V., Efficacy and safety of intrauterine insemination in patients with moderate to severe endometriosis; a 5 year cohortstudy, systematic review and meta-analysis, Human reproduction (Oxford, England), 28, i221-, 2013	Incorrect study type: retrospective observational study
Kaser,D.J., Goldman,M.B., Fung,J.L., Alper,M.M., Reindollar,R.H., 20150127, When is clomiphene or gonadotropin intrauterine insemination futile? Results of the Fast Track and Standard Treatment Trial and the Forty and Over Treatment Trial, two prospective randomized controlled trials, Fertility & Sterility, 102, 1331-1337, 2014	Incorrect comparison (conventional vs accelerated access to IVF).

Study	Reason for Exclusion
Nappi,L., Carriero,C., Efficacy of super ovulatory drugs and intrauterine insemination in the management of infertility, Italian Journal of Gynaecology and Obstetrics., 12, 154-156, 2000	Incorrect study type: Narrative review.
Tjon-Kon-Fat,R.Bensdorp AJ Mol, The natural conception rate in couples with unexplained or mild male subfertility scheduled for treatment with IVF-SET, IVF-MNC or IUI-COH (INeS trial), Human reproduction (Oxford, England), 29 suppl 1, i214-i234, 2014	Abstract only: no full text article available.
Veltman-Verhulst,S.M., Cohlen,B.J., Hughes,E., Heineman,M.J., 20121030, Intra-uterine insemination for unexplained subfertility. [Review][Update of Cochrane Database Syst Rev. 2006;(4):CD001838; PMID: 17054143], Cochrane Database of Systematic Reviews, 9, CD001838-, 2012	Systematic review that does not match review protocol (comparison included ovarian stimulation). Used for cross checking as appropriate.

Appendix G: Evidence tables

Table 6: Bhattacharya 2008

Bibliographic reference	**Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulatedintrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337, pp.a716, -, 2008**
Study type	Randomised controlled trial
Aim	To compare the effectiveness of clomiphene citrate* and unstimulated IUI with expectant management for the treatment of unexplained infertility * This comparison does not meet the review criteria and therefore is not reported here.
Patient characteristics	**Inclusion criteria** • at least 2 years of infertility • bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography) • ovulation demonstrated by appropriately timed mid-luteal progesterone • normal semen variables **Exclusion criteria** Not reported **Baseline Characteristics:** **Mean Age years (±SD):** IUI = 32 (± 3.7) Expectant management = 32 (± 3.4) **Median duration of infertility in months (range):** IUI = 30 (25-40) Expectant management = 30 (25-38) **Infertility diagnosis (%)** Pure unexplained infertility: n = 332 (86%) IUI = 165/191 Expectant management = 167/193 Mild male infertility factor infertility and/or mild endometriosis: n = 57 (14%) IUI = 28/191

Bibliographic reference	**Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulatedintrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337, pp.a716, -, 2008**
	Expectant management = 29/193
Number of Patients	N (total) = 386 couples IUI (unstimulated)= 193 Expectant management = 193
Intervention	IUI (unstimulated)
Comparison	Expectant management (EM) *a third group was included in the trial who received clomiphene citrate. However, this comparison does not meet the review criteria and therefore is not reported here.
Methods	**Study dates** September 2001 - September 2005 **IUI:** Women were asked to monitor mid-morning urinary LH from day 12 of their cycle using Clearview (Unipath, Bedford). A single insemination was performed 20-30h after endogenous LH surge was detected. Couples were advised to avoid intercourse from day 12 of the cycle until the day of the IUI **Expectant management EM:** This involved 6 months during which no clinic visits or medical interventions were scheduled. Couples were given general advice regarding the need for regular intercourse, but no specific measures such as basal temperature charts or LH kits were recommended
Length of follow up	Treatment duration: 6 months
Location	Scotland
Outcomes measures and effect size	**Live birth (all):** IUI = 43/191 (23%) EM= 32/193 (17%) **Live birth (subgroups:)** **Live birth (unexplained infertility):** IUI = 38/165 (23%) EM= 26/167 (16%)

Bibliographic reference	Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulatedintrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337, pp.a716, -, 2008
	Live birth (Mild male factor): IUI = 2/14 (14%) EM= 2/9 (22%) **Live birth (Mild endometriosis):** IUI=3/13 (23%) EM=4/17 (22%) **Live birth (Mild endometriosis and mild male factor):** IUI=0/1 EM=0/0 **Pregnancy per women (all):** IUI = 43/191 (23%) EM= 33/193 (17%) **Multiple pregnancy per women (all):** IUI = 1/191 (1%) EM= 2/193 (1%) **Pregnancy related adverse events:** **Miscarriage/pregnancy (all):** IUI = 9/55 (10%) EM= 14/46 (30%) **Ectopic/pregnancy (all):** IUI = 2/55 (4%) EM= 1/46 (2%) **Preterm birth/pregnancy (all):** IUI = 6/43 (14%) EM= 5/31 (16%) **Patient related adverse events:** **Treatment related hospital admissions:** IUI = 0/163 (0%) EM= 2/160 (1%)

Bibliographic reference	Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulatedintrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337, pp.a716, -, 2008
	Abdominal pain: IUI = 12/164 (7%) EM= 5/159 (3%) **Vaginal bleeding:** IUI = 10/164 (6%) EM= 4/159 3%) **Nausea:** IUI = 3/164 (2%) EM = 4/159 (3%) **Vomiting:** IUI = 0/164 (0%) EM= 0/158 (0%) **Headache:** IUI = 4/164 (3%) EM= 6/159 (4%) **Hot flushes:** IUI = 0/164 (0%) EM= 4/159 (3%) **Bloating:** IUI = 6/164 (4%) EM = 0/158 (0%) **Process of treatment acceptable (patient satisfaction)** IUI = 155/162 (96%) EM= 123/153 (80%) **Outcome of treatment acceptable (patient satisfaction)** IUI = 117/159 (74%) EM = 82/148 (55%) **Anxiety:** IUI = 22/173 (13%) EM= 31/171 (18%) **Depression:** IUI = 2/172 (1%) EM= 4/170 (3%)

Bibliographic reference	**Bhattacharya,S., Harrild,K., Mollison,J., Wordsworth,S., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Clomifene citrate or unstimulatedintrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial, BMJ (Clinical research ed.), Vol.337, pp.a716, -, 2008**
Source of funding	Chief Scientist Office, Scotland
Comments	**Limitations:** - An independent statistician generated the randomisation allocation sequence. Research nurses enrolled participants in each centre and assigned them to their groups using a central telephone randomisation system (the coordinating centre). The minimisation algorithm balanced allocation of treatment by age, parity and duration of subfertility. Women were stratified by centre. - Because of the nature of the intervention blinding was not possible. - Sample size calculation was performed (95% power at the 5% level of significance to detect a difference in live birth rates of 20% (10% to 30%; odds ratio 4) between expectant and unstimulated IUI. - Couples with mild male factor infertility (minimum sperm motility of 20%) and or minimal endometriosis were also included in the study (14% of sample in the IUI versus EM group) - 17% of women allocated to IUI (n = 33) received alternative treatment (EM) and 3% of women in the EM group (n = 6) received alternative treatment (IUI) - Analysis was on an intention to treat basis (based on allocated treatment) - 2 from the IUI group and 0 from the expectant management group were lost to follow up Risk of bias: lack of blinding. Applicability: outcome ‘live birth’ indirect for live singleton birth. **Other information:** Clinical pregnancy was defined as the presence of an intrauterine gestational sac on ultrasonography, with a fetal heartbeat five weeks

Table 7: Cohlen 1998

Bibliographic reference	**Cohlen,B.J., te Velde,E.R., van Kooij,R.J., Looman,C.W., Habbema,J.D., Controlled ovarian hyperstimulation and intrauterine insemination for treating male subfertility: a controlled study, Human Reproduction, 13, 1553-1558, 1998**
Study type	Randomised controlled trial
Aim	To determine whether the use of controlled ovarian hyperstimulation with low-dose human menopausal gonadotrophin in couples with male subfertility leads to a higher probability of conception when intrauterine insemination (IUI) is applied. Cross-over, alternating design with pre-cross over data available and extracted here.

Bibliographic reference	**Cohlen,B.J., te Velde,E.R., van Kooij,R.J., Looman,C.W., Habbema,J.D., Controlled ovarian hyperstimulation and intrauterine insemination for treating male subfertility: a controlled study, Human Reproduction, 13, 1553-1558, 1998**
Patient characteristics	**Inclusion criteria** • Male subfertility defined as (in at least 2 semen samples): concentration < 20 million/mL and/or motility < 40 % and /or normal morphology < 40%. • Women had regular (25-35 day) cycles • Women must have had biphasic basal body temperature • Mid luteal progesterone concentration of >=9.7 ng/ml • No abnormalities on hysterosalpingography and/or laparoscopy that could explain infertility **Exclusion criteria** • Men with antisperm antibodies • Cervical factor to infertility **Baseline Characteristics:** Age of the women: 30.7ys (range: 24-39). Duration of subfertility: 3.1 ys (range 2-9). Ovulatory status: BBT, NLP Tubal patency: HSG and/or DLS. PCT: done to exclude cervical factor. No antibodies in semen.
Number of Patients	IUI + ovarian stimulation: 36 couples IUI without ovarian stimulation: 38 couples
Intervention	IUI + ovarian stimulation (human menopausal
Comparison	IUI without ovarian stimulation
Methods	Cross-over, alternating design with pre-cross over data available and extracted here. **IUI + ovarian stimulation** 75 IU hMG/day up to 150 IU/day max. (day 3- Ovulation induction: 5,000 IU hCG. **General** Estimation of ovulation: LH in blood and ultrasound. Cancellation criteria: > 3 follicles > 17 mm and E2 > 6,000 pmol/L, premature LH surge, no LH surge detected. Timing: OH cycle: 38-40 hrs after hCG. Natural / OH cycle with premature LH surge: 26 hrs after detecting LH-rise.

Bibliographic reference	**Cohlen,B.J., te Velde,E.R., van Kooij,R.J., Looman,C.W., Habbema,J.D., Controlled ovarian hyperstimulation and intrauterine insemination for treating male subfertility: a controlled study, Human Reproduction, 13, 1553-1558, 1998**
	Sperm preparation: Wash (Ham's F10) and Percoll. Number of IUI per cycle: 1.
Length of follow up	Treatment duration: single cycle (up to 6 cycles were performed, but with an alternating cross over design; only data for the first cycle was extracted here)
Location	The Netherlands
Outcomes measures and effect size	**Pregnancy rates/ cycle (confirmed by ultrasound at 6/7 weeks gestation)** IUI with stimulation = 3/36 (8.3%) IUI without stimulation = 4 /38 (10.5%)
Source of funding	OrganonNederland B.V.
Comments	**Limitations:** Cross-over design so only data from pre-crossover (data from only 1 cycle) reported. This impacts on statistical power of study. Risk of bias: blinding not reported. Applicability: none. **Other information:** Randomisation was by opaque, sealed envelopes

Table 8: Goverde 2005

Bibliographic reference	**Goverde,A.J., Lambalk,C.B., McDonnell,J., Schats,R., Homburg,R., Vermeiden,J.P.W., Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: Effects on pregnancy and multiple pregnancy rates, Human Reproduction, 20, 3141-3146, 2005** **Goverde,A.J., McDonnell,J., Vermeiden,J.P.W., Schats,R., Rutten,F.F.H., Schoemaker,J., Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: A randomised trial and cost-effectiveness analysis, Lancet, 355, 13-18, 2000**
Study type	Randomised controlled trial
Aim	To investigate data from an earlier prospective trial (Goverde et al., 2000) with regard to the specific question of whether the application of mild hyperstimulation in IUI cycles could be an alternative strategy for obtaining

Bibliographic reference	**Goverde,A.J., Lambalk,C.B., McDonnell,J., Schats,R., Homburg,R., Vermeiden,J.P.W., Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: Effects on pregnancy and multiple pregnancy rates, Human Reproduction, 20, 3141-3146, 2005** **Goverde,A.J., McDonnell,J., Vermeiden,J.P.W., Schats,R., Rutten,F.F.H., Schoemaker,J., Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: A randomised trial and cost-effectiveness analysis, Lancet, 355, 13-18, 2000**
	acceptable pregnancy rates while preventing a high multiple pregnancy rate, compared with natural cycles for IUI
Patient characteristics	**Inclusion criteria** • Couples with unexplained infertility for at least 3 years or: • Mild to moderate male subfertility for at least 1 year **Exclusion criteria** • If the woman had cycle disorders • Untreated endometriosis (American Fertility Society criteria grade 2-4) • Bilateral occluded tubes • Partner's semen sample yielded less than 1 million progressively motile spermatozoa after processing/centrifugation • >20% of spermatozoa carried antibodies • If more than 50% of spermatozoa had no acrosome **Baseline Characteristics:** **Age ±SD in years** IUI + FSH = 31.7 ± 3.9 IUI = 31.6 ± 3.7 **Duration of infertility ±SD in years** IUI + FSH = 4.2 ± 1.9 IUI = 3.9 ± 1.7 **Diagnosis of cause of infertility (%)** Unexplained infertility: n= 120/171 (70.2%) IUI + FSH = 61/85 (71.8%) IUI = 59/86 (68.6%) Male subfertility: n =51/171 (29.8%) IUI + FSH = 24/85 (28.2%) IUI = 27/86 (31.4%)
Number of Patients	N = 171 couples

Bibliographic reference	**Goverde,A.J., Lambalk,C.B., McDonnell,J., Schats,R., Homburg,R., Vermeiden,J.P.W., Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: Effects on pregnancy and multiple pregnancy rates, Human Reproduction, 20, 3141-3146, 2005** **Goverde,A.J., McDonnell,J., Vermeiden,J.P.W., Schats,R., Rutten,F.F.H., Schoemaker,J., Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: A randomised trial and cost-effectiveness analysis, Lancet, 355, 13-18, 2000**
	IUI + FSH = 85 IUI = 86
Intervention	IUI + FSH
Comparison	IUI timed to spontaneous ovulation
Methods	**Study dates** February 1992 - September 1995 **IUI + FSH** The stimulation protocol stipulated a low dose of FSH in order to limit the number of dominant follicles to ≤3, with the goal of optimizing the pregnancy rate while preventing a high multiple pregnancy rate. Baseline pelvic US was done at cycle day 3 and 75IU of FSH was injected daily until transvaginal US showed at least one follicle with a diameter of 18mm. Patients tested their urine twice daily (morning and evening void) for the occurrence of an LH surge. In the event of such surge, 10000IU of hCG was given as soon as possible, and a single IUI was done 20-30h after the detection of the surge. When no LH surge was detected in the presence of at least one follicle with a diameter of 8mm or more, 10000IU of hCG was given and a single IUI was done 40-42h later **IUI timed to spontaneous ovulation** Women underwent a basal transvaginal US assessment at the beginning of their menstrual period, and on the 10th day of the cycle. Patients tested their urine sample twice daily (second morning void and between 18:00 and 19:00) for the occurrence of the endogenous LH surge. As soon as they had detected the LH surge, patients contacted the clinic and ultrasonography was performed to assess follicular development. A single IUI was done 20-30h after the detection of the LH peak
Length of follow up	Treatment duration: 4 treatment cycles
Location	Netherlands

Bibliographic reference	**Goverde,A.J., Lambalk,C.B., McDonnell,J., Schats,R., Homburg,R., Vermeiden,J.P.W., Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: Effects on pregnancy and multiple pregnancy rates, Human Reproduction, 20, 3141-3146, 2005** **Goverde,A.J., McDonnell,J., Vermeiden,J.P.W., Schats,R., Rutten,F.F.H., Schoemaker,J., Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: A randomised trial and cost-effectiveness analysis, Lancet, 355, 13-18, 2000**
Outcomes measures and effect size	**Live birth** IUI + FSH = 31/85 (36.5%) IUI = 25/86 (29.1%) **Live singleton birth (calculated from study)** IUI + FSH = 22/85 (36.5%) IUI = 25/86 (29.1%) **Ongoing pregnancy** IUI + FSH = 33/85 (38.8%) IUI = 28/86 (32.6%) **Singleton pregnancy** IUI + FSH = 24/85 (28.2%) IUI = 27/86 (31.4%) **Multiple pregnancy** IUI + FSH = 9/85 (10.6%) IUI = 1*/86 (1.2%) *** one monozygotic twin pregnancy but both twins were stillborn after premature rupture of membranes**
Source of funding	Financial support by the Health Insurance Executive Board, Amstelveen, Netherlands

Bibliographic reference	**Goverde,A.J., Lambalk,C.B., McDonnell,J., Schats,R., Homburg,R., Vermeiden,J.P.W., Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: Effects on pregnancy and multiple pregnancy rates, Human Reproduction, 20, 3141-3146, 2005** **Goverde,A.J., McDonnell,J., Vermeiden,J.P.W., Schats,R., Rutten,F.F.H., Schoemaker,J., Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: A randomised trial and cost-effectiveness analysis, Lancet, 355, 13-18, 2000**
Comments	**Limitations:** - Method of randomisation: computer-generated randomisation schedule, administered by numbered masked and sealed envelopes - Power calculation for pregnancy rate per cycle Risk of bias: blinding not reported. Applicability/indirectness: outcome 'live birth' indirect for live singleton birth. **Other information:** - Unexplained infertility as defined as couples with no abnormality found during extensive investigation of infertility, including basal body temperature chart, a late luteal phase endometrial biopsy, a post-coital test, a hysterosalpingogram, a diagnostic laparoscopy, and at least two semen analysis - Male subfertility was diagnosed if at least 3 out of 5 semen analysis showed a total motile sperm count of fewer than $20X10^6$ progressively motile spermatozoa in the ejaculate and if the remainder of the infertility investigation revealed no additional abnormalities - The administration of hCG was withheld and IUI was not performed when more than 3 follicles ≥18 mm or more than 6 follicles ≥14mm were present - Pregnancy was defined as ongoing pregnancy with at least one fetal heartbeat at 12 weeks of gestation - Multiple pregnancy was defined as more than one fetal heartbeat at 12 weeks gestation

Table 9: Guzick 1999

Bibliographic reference	**Guzick,D.S., Carson,S.A., Coutifaris,C., Overstreet,J.W., Factor-Litvak,P., Steinkampf,M.P., Hill,J.A., Mastroianni,L., Buster,J.E., Nakajima,S.T., Vogel,D.L., Canfield,R.E., Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine network, New England Journal of Medicine, 340, 177-183, 1999**
Study type	Randomised controlled trial
Aim	To report on the efficacy of superovulation and IUI
Patient characteristics	**Inclusion criteria**

Bibliographic reference	Guzick,D.S., Carson,S.A., Coutifaris,C., Overstreet,J.W., Factor-Litvak,P., Steinkampf,M.P., Hill,J.A., Mastroianni,L., Buster,J.E., Nakajima,S.T., Vogel,D.L., Canfield,R.E., Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine network, New England Journal of Medicine, 340, 177-183, 1999
	• Age ≤40 years for women and ≤55 years for men • Negative pregnancy test • Normal pelvis and uterine cavity • 'in phase' endometrial biopsy • negative serum antisperm antibody test • normal FSH and Thyrotropin on days 1-5 of cycle • regular cycles • history of infertility >1 year • Presence of any motile sperm on screening semen analysis **Exclusion criteria** • Previous use of IVF or other ART • Previous treatment with gonadotrophins • previous IUI with current partner • History of chronic disease • History of chemotherapy or radiation to the abdomen or pelvis • History of tubal surgery • Extensive tubal adhesions • Endometriosis of more than stage II • History of myomectomy, ovarian cystectomy or unilateral oophorectomy • History of male vasovasostomy • Male varicocelectomy within 6 months before study • History of pelvic-node dissection **Baseline Characteristics:** **Women's Age ±SD years:** IUI + superovulation = 32 ±4 IUI alone = 32 ±4 **Duration of infertility (months):** IUI + superovulation = 42±26

Bibliographic reference	**Guzick,D.S., Carson,S.A., Coutifaris,C., Overstreet,J.W., Factor-Litvak,P., Steinkampf,M.P., Hill,J.A., Mastroianni,L., Buster,J.E., Nakajima,S.T., Vogel,D.L., Canfield,R.E., Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine network, New England Journal of Medicine, 340, 177-183, 1999**
	IUI alone = 46±31
Number of Patients	n = 465 couples/2301 cycles IUI + superovulation: 231 (618 cycles) IUI: 234 (717 cycles)
Intervention	IUI + superovulation (FSH stimulation)
Comparison	IUI timed to spontaneous ovulation
Methods	Study dates: not reported Eligible couples were randomly assigned to one of 4 groups: intracervical insemination timed to the surge of LH, IUI timed to the surge of LH, superovulation + intracervical insemination or superovulation and IUI. Only comparisons included IUI (not intracervical insemination) were extracted. Each couple received 4 treatment cycles unless they became pregnant in the 1st 2nd or 3rd cycle. Rest cycles could occur between treatment cycles for personal or medical reasons. Cycles were cancelled in the superovulation group if day 3 serum estradiol exceeded 3000 pg per ml. Cycles were cancelled in the unstimulated group if there was no luteinising hormone surge. Women assigned to the superovulation group were treated according to a standard protocol where FSH was administered from day 3 to 7. Daily administration of FSH was continued, with the dose adjusted if necessary, until at least 2 follicles reached ≥18 mm and E2 concentration ranged from 500 to 3000pg/ml. Once these criteria were met, treatment with FSH was discontinued and 10 000IU of hCG was administered. A single insemination was performed 36 to 40 hours later. For the IUI timed to spontaneous ovulation group, insemination was timed to the day after the spontaneous luteinising hormone surge (detected by urine testing kit).
Length of follow up	Treatment duration: up to 4 treatment cycles (fewer cycles if pregnancy occurred in the 1st, 2nd or 3rd cycle)
Location	US (multicentre)

Bibliographic reference	**Guzick,D.S., Carson,S.A., Coutifaris,C., Overstreet,J.W., Factor-Litvak,P., Steinkampf,M.P., Hill,J.A., Mastroianni,L., Buster,J.E., Nakajima,S.T., Vogel,D.L., Canfield,R.E., Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine network, New England Journal of Medicine, 340, 177-183, 1999**
Outcomes measures and effect size	**Pregnancy rate per couple (defined as presence of serum β-hCG measured 15 days after IUI with an increase in serum β-hCG 2 days later, during treatment period per women)** IUI + superovulation: 77/231 (33.3%) IUI: 42/234 (17.9%) **Term live birth** IU I + superovulation: 41/231 IUI: 28/234 **Preterm birth** IUI + superovulation: 9/231 IUI: 2/234 **Stillbirth** IUI+ superovulation: 0/231 IUI: 1/234 **Miscarriage:** IUI+ superovulation: 22/231 IUI: 6/234 **Induced abortion:** IUI+ superovulation: 0/231 IUI: 1/234 **Ectopic:** IUI+ superovulation: 4/231 IUI:2/234 **Multiple pregnancy:** **Quadruplets:** IUI+ superovulation:: 2/231 IUI: 0/234 **Triplets:** IUI+ superovulation:: 3/231 IUI: 0/234
Source of funding	Cooperative Agreements with the National Institute of Child Health and Human Development and by Serono Laboratories

Bibliographic reference	**Guzick,D.S., Carson,S.A., Coutifaris,C., Overstreet,J.W., Factor-Litvak,P., Steinkampf,M.P., Hill,J.A., Mastroianni,L., Buster,J.E., Nakajima,S.T., Vogel,D.L., Canfield,R.E., Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine network, New England Journal of Medicine, 340, 177-183, 1999**
Comments	**Limitations:** Only biochemical pregnancies are reported (not confirmed by ultrasound) The number of cancelled cycles was higher in the unstimulated group (98/1002) than the superovulation group (32/1299). The number of rest cycles was greater in the superovulation group (698/1378) than the unstimulated group (187/1002). Withdrawal rate from the study higher in the superovulation group (18%) than the unstimulated group (9%). Cycles in the superovulation group were less likely to be consecutive, and so were in the study for a longer time period on average. Risk of bias: blinding not reported. Applicability/indirectness: outcome of 'live birth' indirect for 'live singleton birth' **Other information:** 17 of 18 sets of twins were in the superovulation groups, however the authors do not report which group (intrauterine or intracervical stimulation) and so this data could not be extracted. 6 women had OHSS requiring hospitalization. During treatment 72 couples (IUI + COH = 50 and IUI alone = 22) withdrew for reasons related to treatment (i.e., absence of response to COH, OHSS and anovulatory cycles for two consecutive cycles) or for reasons not related to treatment (i.e. other medical problems, desire to adopt a child and the cost of treatment).

Table 10: Steures 2006

Bibliographic reference	**Steures,P., van der Steeg,J.W., Hompes,P.G., Habbema,J.D., Eijkemans,M.J., Broekmans,F.J., Verhoeve,H.R., Bossuyt,P.M., van,der,V, Mol,B.W., Collaborative Effort on the Clinical Evaluation in Reproductive Medicine, Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial, Lancet, 368, 216-221, 2006**
Study type	Randomised controlled trial
Aim	To assess the effectiveness of intrauterine insemination with controlled ovarian stimulation compared to expectant management in couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy in the next 12 months

Bibliographic reference	**Steures,P., van der Steeg,J.W., Hompes,P.G., Habbema,J.D., Eijkemans,M.J., Broekmans,F.J., Verhoeve,H.R., Bossuyt,P.M., van,der,V, Mol,B.W., Collaborative Effort on the Clinical Evaluation in Reproductive Medicine, Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial, Lancet, 368, 216-221, 2006**
Patient characteristics	**Inclusion criteria** • the couple had not conceived after at least a year of frequent unprotected intercourse • the woman <39 years • woman with regular cycles • the couple had an intermediate prognosis of spontaneous ongoing pregnancy within the next month (intermediate prognosis was defined as the chance of spontaneous ongoing **Exclusion criteria** Not reported **Baseline Characteristics:** **Mean age years (±SD; range)** IUI + gonadotrophins = 33 (±3.4; 23 - 40) Expectant management= 33 (±3.1; 24 - 38) **Mean duration of subfertility years (±SD; range)** IUI + gonadotrophins = 2.0 (±0.5; 1 - 3) Expectant management = 1.9 (±0.5; 1 - 3)
Number of Patients	n = 253 couples IUI + gonadotrophins = 127 Expectant management = 126
Intervention	IUI + ovarian stimulation (FSH or human menopausal gonadotropin)
Comparison	Expectant management
Methods	**Study dates** June 1, 2002 - July 1, 2005 Couples were randomly assigned to IUI + gonadotrophins or expectant management for 6 months. **IUI + FSH or hMG** Couples assigned to IUI + gonadotrophins started treatment during the next menstrual cycle. Gonadotrophins, semen preparation and IUI regimens were done according to hospital specific protocols. Baseline transvaginal US was done on cycle day 3 to exclude ovarian cysts >20 mm. Thereafter women started daily injections of FSH or

Bibliographic reference	**Steures,P., van der Steeg,J.W., Hompes,P.G., Habbema,J.D., Eijkemans,M.J., Broekmans,F.J., Verhoeve,H.R., Bossuyt,P.M., van,der,V, Mol,B.W., Collaborative Effort on the Clinical Evaluation in Reproductive Medicine, Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial, Lancet, 368, 216-221, 2006**
	hMG until transvaginal US showed at least 1 follicle of at least 16mm in diameter. Ovulation was induced with hCG and women were inseminated 36-40h later. Cycles were cancelled if there were >3 follicles of diameter >16mm or >5 of diameter >12mm. **Expectant management** Couples assigned to expectant management were followed up until an ongoing pregnancy occurred or for 6 months if no pregnancy occurred.
Length of follow up	Treatment duration: 6 months
Location	The Netherlands
Outcomes measures and effect size	**Live birth, 6 months:** IUI + gonadotrophins = 26/127 (21.0%) Expectant management = 31/126 (24.6%) **Pregnancy (Clinical/ongoing), 6 months:** IUI + gonadotrophi31n127s = 29/127 (22.8%) Expectant management = 30/126 (23.8%) **Multiple pregnancies, 6 months:** IUI + gonadotrophins = 2/127 (1.6%) Expectant management = 1/126 (0.8%) **Pregnancy related adverse events, 6 months:** **Miscarriage:** IUI + gonadotrophins = 13/42 (30.9%) Expectant management = 6/40 (15.0%) **Ectopic pregnancies:** IUI + gonadotrophins = 1/127 (0.8%) Expectant management = 1/126 (0.8%)
Source of funding	ZonMW (The Netherlands Organization for Health Research and Development, The Hague, Netherlands)

Bibliographic reference	**Steures,P., van der Steeg,J.W., Hompes,P.G., Habbema,J.D., Eijkemans,M.J., Broekmans,F.J., Verhoeve,H.R., Bossuyt,P.M., van,der,V, Mol,B.W., Collaborative Effort on the Clinical Evaluation in Reproductive Medicine, Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial, Lancet, 368, 216-221, 2006**
Comments	**Limitations:** The randomisation sequence was computer generated in balanced block multiples of 2 or 4, stratified by centre. The sequence was concealed, and sealed opaque envelopes containing details of the treatment allocation were assembled by an independent person. No blinding reported - Sample size calculation was performed (80% power at 5% level of significance to detect a difference in ongoing pregnancy rates of 13% between expectant management and stimulated IUI - 25 (20%) women in the expectant management group started IUI before 6 months - 17 (7%) men had a sperm motility count of <10 million, 7 in the intervention group and 10 in the expectant management group (male factor infertility) - In 31 (24%) women assigned to the intervention group and in 32 (25%) assigned to expectant management group, tubal function had not been assessed by hysterosalpingography or laparoscopy before randomisation. In some couples participating in the study, cases of endometriosis and tubal pathology could not be ruled out since hysterosalpingography or laparoscopy were not done - The study protocol recommended use of gonadotrophins for ovarian stimulation, however in 11% of cycles clomifene citrate was used - In the IUI + gonadotrophins group there were 6 spontaneous pregnancies before IUI; one miscarried. 7 conceived spontaneously between IUI; one miscarried - 5.2% (5/96) in the IUI group and 2.3% (2/84) in the expectant management group had unilateral tubal block - Analysis was on an intention to treat basis. Risk of bias: blinding not reported. Applicability/indirectness: outcome 'live birth' indirect for live singleton birth. **Other information:** Tubal pathology was judged to be absent if the chlamydia antibody test was negative or subsequent hysterosalpingography, laparoscopy, or both showed two normal patent tubes. Those for whom the tubal function had been assessed only by chlamydia antibody test at the time of randomisation sometimes would have a hysterosalpingography or laparoscopy before the first cycle of gonadotrophins or after 3 cycles of treatment. Ongoing pregnancy was defined as the presence of fetal cardiac activity at transvaginal sonography at a duration of gestation of at least 12 weeks.

Table 11: Tummon 1997

Bibliographic reference	**Tummon,I.S., Asher,L.J., Martin,J.S., Tulandi,T., Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis, Fertility and Sterility, 68, 8-12, 1997**
Study type	Randomised controlled trial
Aim	Evaluate the efficacy of superovulation and IUI versus no treatment for infertility associated with minimal or mild endometriosis.
Patient characteristics	**Inclusion criteria** • Female age 20 to 39 years • regular menstruation and evidence of ovulation • normal serum PRL • normal TSH • bilateral tubal patency • minimal or mild endometriosis diagnosed visually via laparoscopy in 12 months before enrolment • total motile count >40*106 on semen screening. • Informed consent from both partners. **Exclusion criteria** • Hormonal endometriosis therapy in 6 months before enrolment • ovulation induction within 3 months • previous ovulation induction with gonadotrophins • female body weight <52kg or >88kg. • Day-3 FSH level => 20 mIU/mL **Baseline Characteristics:** **Superovulation plus IUI group** Previous surgical reduction performed (%): 47 Female age (years): 31.2 (SD 4.5) Duration of infertility (months): 43 (SD 26) **No treatment group:** Previous surgical reduction performed (%): 68 Female age (years): 30.6 (SD 3.3) Duration of infertility (months): 42 (SD 22)

Bibliographic reference	**Tummon,I.S., Asher,L.J., Martin,J.S., Tulandi,T., Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis, Fertility and Sterility, 68, 8-12, 1997**
Number of Patients	117 couples agreed to join study. 58 in superovulation plus IUI arm and 59 in the no treatment arm. Results are reported for 53 (91%) from the superovulation and IUI arm and 50 (85%) from the no treatment arm. The numbers entering each treatment cycle were 53, 39, 27 and 8 for the superovulation arm and 50, 48,44 and 42 for the no treatment arm.
Intervention	**IUI + ovulation stimulation: Menstrual day 3 a daily IM injection of FSH. Initial dose of => 75 IU adjusted for weight and age. Dose adjusted after monitoring until at least 1 follicle >1.8cm. Final trigger with IM injection of 5,000 IU of hCG. IUI sample prepared and transferred approximately 20 hours after trigger.**
Comparison	**No treatment:** no information given.
Methods	**Study dates** Couples were recruited between December 1990 to September 1993
Length of follow up	Unclear: Up to 4 cycles. 53 couples underwent 127 treatment cycles in the superovulation plus IUI group, and 50 couples underwent 184 cycles of no treatment. Not clear how it was decided whether or not to proceed with the next cycle or not. Cycles were consecutive in time for the expectant management group, but not necessarily for the IUI group.
Location	Canada
Outcomes measures and effect size	**Live births (determined by interview, cumulative number after up to 4 cycles)** Superovulation plus IUI group = 14 of 53 No treatment = 4 of 50 **Live singleton births (calculated by reviewer from number of live births and number of live multiple births, below)** Superovulation plus IUI group = 11 of 53 No treatment = 4 of 50 **Live multiple births (determined by interview, cumulative number after up to 4 cycles)** Superovulation plus IUI group = 3 of 53 No treatment = 0 of 50 **OHSS (cumulative number after up to 4 cycles)** Superovulation plus IUI group = 0 of 53 No treatment = 0 of 50 **No other outcomes reported**

Bibliographic reference	**Tummon,I.S., Asher,L.J., Martin,J.S., Tulandi,T., Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis, Fertility and Sterility, 68, 8-12, 1997**
Source of funding	Canada
Comments	**Limitations:** Study design and analysis was based on cycles rather than couples. This can introduce bias as couples with failed cycles are more likely to have failed cycles in the future. Couples with greater than 4 follicles at 1.8cm or greater were offered IVF-ET. Method of randomisation was not described. Blinding was not described. Relatively high dropout rate from no treatment arm. Nine couples either did not start or were ineligible. Significantly greater number had previous surgical reduction for endometriosis in no-treatment group. Not clear how it was decided whether or not to proceed with the next cycle or not. Appears to be a high dropout rate in the superovulation arm that is unrelated to number of pregnancies in previous cycles. Cycles were consecutive in time for the expectant management group, but not necessarily for the IUI group. Risk of bias: blinding not reported. Applicability: outcome ‘live birth’ indirect for live singleton birth.

Appendix H: GRADE profiles

Table 12: Grade profile for IUI without ovarian stimulation versus expectant management

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI	Expectant management	Relative (95% CI)	Absolute	Quality
Live birth (all)											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	very serious[3]	serious[4]	none	43/191 (22.5%)	32/193 (16.6%)	RR 1.36 (0.9 to 2.05)	60 more per 1000 (from 17 fewer to 174 more)	VERY LOW
Live birth (unexplained infertility)											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	very serious[3,5]	serious[4]	none	38/165 (23%)	26/167 (15.6%)	RR 1.48 (0.94 to 2.32)	75 more per 1000 (from 9 fewer to 206 more)	VERY LOW
Live birth (mild male factor)											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	very serious[3,5]	very serious[6]	none	2/14 (14.3%)	2/9 (22.2%)	RR 0.64 (0.11 to 3.78)	80 fewer per 1000 (from 198 fewer to 618 more)	VERY LOW
Live birth (mild endometriosis)											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	very serious[3,5]	very serious[6]	none	3/13 (23.1%)	4/17 (23.5%)	RR 0.98 (0.26 to 3.64)	5 fewer per 1000 (from 174 fewer to 621 more)	VERY LOW
Live birth - Live birth (mild endometriosis and mild male factor)											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	very serious[3,5]	no serious imprecision[7]	none	0/1 (0%)	NC	NC	NC	VERY LOW
Pregnancy rate - Pregnancy per woman (all)											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	serious[4]	none	43/191 (22.5%)	33/193 (17.1%)	RR 1.32 (0.88 to 1.98)	55 more per 1000 (from 21 fewer to 168 more)	VERY LOW
Pregnancy rate - multiple pregnancies per woman (all)											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	1/191 (0.52%)	2/193 (1%)	RR 0.51 (0.05 to 5.53)	5 fewer per 1000 (from 10 fewer to 47 more)	VERY LOW
Pregnancy related adverse events - Miscarriage per pregnancy											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	serious[4]	none	9/55 (16.4%)	14/46 (30.4%)	RR 0.54 (0.26 to	140 fewer per 1000 (from 225	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI	Expectant management	Relative (95% CI)	Absolute	
									1.13)	fewer to 40 more)	
Pregnancy related adverse events - Ectopic pregnancy per pregnancy											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	2/55 (3.6%)	1/46 (2.2%)	RR 1.67 (0.16 to 17.86)	15 more per 1000 (from 18 fewer to 367 more)	VERY LOW
Pregnancy related adverse events - Preterm birth											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	6/43 (14%)	5/31 (16.1%)	RR 0.87 (0.29 to 2.58)	21 fewer per 1000 (from 115 fewer to 255 more)	VERY LOW
Patient related adverse events - Treatment related hospital admissions											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	0/163 (0%)	2/160 (1.3%)	RR 0.2 (0.01 to 4.06)	10 fewer per 1000 (from 12 fewer to 38 more)	VERY LOW
Patient related adverse events - Abdominal pain											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	serious[4]	none	12/164 (7.3%)	5/159 (3.1%)	RR 2.33 (0.84 to 6.45)	42 more per 1000 (from 5 fewer to 171 more)	VERY LOW
Patient related adverse events - Vaginal bleeding											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	serious[4]	none	10/164 (6.1%)	4/159 (2.5%)	RR 2.42 (0.78 to 7.57)	36 more per 1000 (from 6 fewer to 165 more)	VERY LOW
Patient related adverse events - Nausea											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	3/164 (1.8%)	0/158 (0%)	RR 0 (0.35 to 129.55)	NC	VERY LOW
Patient related adverse events - Hot flushes											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	0/164 (0%)	4/159 (2.5%)	RR 0.11 (0.01 to 1.99)	22 fewer per 1000 (from 25 fewer to 25 more)	VERY LOW
Patient related adverse events - Bloating											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	6/164 (3.7%)	0/158 (0%)	RR 12.53 (0.71 to 220.54)	NC	VERY LOW
Patient related adverse events - total											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	serious[4]	none	31/164 (18.9%)	15/159 (9.4%)	RR 2 (1.13 to	94 more per 1000 (from 12 more to	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI	Expectant management	Relative (95% CI)	Absolute	Quality
									3.57)	242 more)	
Patient satisfaction - Process of treatment acceptable											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	serious[4]	none	155/162 (95.7%)	123/153 (80.4%)	RR 1.19 (1.09 to 1.3)	153 more per 1000 (from 72 more to 241 more)	VERY LOW
Patient satisfaction - Outcome of treatment acceptable											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	serious[4]	none	117/159 (73.6%)	82/148 (55.4%)	RR 1.33 (1.12 to 1.58)	183 more per 1000 (from 66 more to 321 more)	VERY LOW
Anxiety											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	no serious imprecision[8]	none	22/173 (12.7%)	3/171 (1.8%)	RR 7.25 (2.21 to 23.77)	110 more per 1000 (from 21 more to 399 more)	LOW
Depression											
1(Bhattacharya 2008)	RCT	serious[1]	no serious inconsistency[2]	serious[5]	very serious[6]	none	2/172 (1.2%)	4/170 (2.4%)	RR 0.49 (0.09 to 2.66)	12 fewer per 1000 (from 21 fewer to 39 more)	VERY LOW

1 Evidence was downgraded by 1 as blinding was not possible.
2 Inconsistency not applicable as no meta-analysis was conducted (outcome is from a single study).
3 Evidence was downgraded by 1 as the outcome 'live birth' is indirect for 'live singleton birth'.
4 Evidence was downgraded by 1 due to 95% CI crossing one MID.
5 Evidence was downgraded by 1 due to indirectness of treatment as 17% of women allocated to IUI (n = 33) received expectant management and 3% of women in the EM group (n = 6) received IUI.
6 Evidence was downgraded by 2 as 95% CIs crossed two MIDs.
7 Effect estimate and 95% CIs not calculable.
8 No serious imprecision as 95% CIs do not cross MIDs.

Table 13: GRADE table for IUI with ovarian stimulation versus expectant management

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with stimulation	Expectant management	Relative (95% CI)	Absolute	Quality Importance
Live births (determined by interview, cumulative number after up to 4 cycles)											
1(Tummon 1997)	RCT	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	14/53 (26.4%)	4/50 (8%)	RR 3.3 (1.16 to	184 more per 1000	VERY LOW

Quality assessment							No of patients		Effect		Quality Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with stimulation	Expectant management	Relative (95% CI)	Absolute	
									9.36)	(from 13 more to 669 more)	
Live singleton births (number of live births - multiple births)											
1(Tummon 1997)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[5]	serious[4]	none	11/53 (20.8%)	4/50 (8%)	RR 2.59 (0.88 to 7.62)	127 more per 1000 (from 10 fewer to 530 more)	LOW
Live multiple births (determined by interview, cumulative number after up to 4 cycles)											
1(Tummon 1997)	RCT	serious[1]	no serious inconsistency[2]	serious[3]	very serious	none	3/53 (5.7%)	0/50 (0%)	RR 6.61 (0.35 to 124.85)	NC	VERY LOW
Live births											
1(Steures 2006)	RCT	serious[1]	no serious inconsistency[2]	serious[3]	very serious[6]	none	26/127 (20.5%)	30/126 (24.6%)	RR 0.86 (0.54 to 1.37)	34 fewer per 1000 (from 113 fewer to 91 more)	VERY LOW
Ovarian hyperstimulation syndrome											
1(Tummon 1997)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[5]	no serious imprecision[7]	none	0/53 (0%)	0/50 (0%)	NC	NC	MODERATE
Pregnancy rates - Pregnancy (ongoing), 6 months											
1(Steures 2006)	RCT	serious[1]	no serious inconsistency[2]	very serious[8, 9]	very serious[6]	none	29/127 (22.8%)	34/126 (23.8%)	RR 00.85 (0.55 to 1.30)	40 fewer per 1000 (from 121 fewer to 81 more)	VERY LOW
Pregnancy rates - Multiple pregnancies, 6 months											
1(Steures 2006)	RCT	serious[1]	no serious inconsistency[2]	serious [8]	very serious[6]	none	2/127 (1.6%)	1/126 (0.79%)	RR 1.98 (0.18 to 21.61)	8 fewer per 1000 (from 7 fewer to 164 more)	VERY LOW
Pregnancy related adverse events - Miscarriage, 6 months											
1(Steures 2006)	RCT	serious[1]	no serious inconsistency[2]	serious[8]	serious[4]	none	13/42 (31%)	6/40 (15%)	RR 2.06 (0.87 to	159 more per 1000	VERY LOW

Quality assessment							No of patients		Effect		Quality Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with stimulation	Expectant management	Relative (95% CI)	Absolute	
									4.9)	(from 20 fewer to 585 more)	

1 Evidence was downgraded by 1 as blinding was not reported.
2 Inconsistency not applicable as no meta-analysis was conducted (outcome is from a single study).
3 Evidence was downgraded by 1 as the outcome 'live birth' is indirect for 'live singleton birth'.
4 Evidence was downgraded by 1 as 95% CIs crossed one MID.
5 No serious indirectness as population, intervention and outcome is in agreement with review protocol.
6 Evidence was downgraded by 2 as 95% CIs crossed two MIDs.
7 No serious imprecision as 95% CI do not cross MIDs.
8 Evidence was downgraded by 1 due to indirect assessment of infertility in 31 (24%) women assigned to the intervention group and in 32 (25%) assigned to expectant management group as tubal function had not been assessed by hysterosalpingography or laparoscopy before randomisation.
9 Evidence was downgraded by 1 due to indirect treatment: 25 couples in expectant management group started IUI during trial duration (6 months).

Table 14: GRADE table for IUI with ovarian stimulation versus IUI without ovarian stimulation

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with stimulation	IUI without stimulation	Relative (95% CI)	Absolute	
Live singleton birth											
1(Goverde 2005)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	22/85 (25.9%)	25/86 (29.1%)	RR 0.89 (0.55 to 1.45)	32 fewer per 1000 (from 131 fewer to 131 more)	VERY LOW
Live births											
2(Goverde 2005, Guzick 1999)	RCT	serious[1]	no serious inconsistency[4]	serious[5]	serious[6]	none	72/316 (22.8%)	53/320 (16.6%)	RR 1.38 (1.01 to 1.88)	63 more per 1000 (from 2 more to 146 more)	VERY LOW
Pregnancy rate per IUI cycle											
1(Cohlen 1998)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	very serious[3]	none	3/36 (8.3%)	4/38 (10.5%)	RR 0.79 (0.19 to 3.29)	22 fewer per 1000 (from 85 fewer to 241	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with stimulation	IUI without stimulation	Relative (95% CI)	Absolute	Quality
										more)	
Pregnancy rate per couple											
1(Guzick 1999)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	no serious imprecision[8]	none	77/231 (33.3%)	42/234 (17.9%)	RR 1.86 (1.34 to 2.58)	154 more per 1000 (from 61 more to 284 more)	MODERATE
Pregnancy rates - Ongoing pregnancy											
1(Goverde 2005)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	serious[6]	none	33/85 (38.8%)	28/86 (32.6%)	RR 1.19 (0.8 to 1.79)	62 more per 1000 (from 65 fewer to 257 more)	LOW
Pregnancy rates - Singleton pregnancy											
1(Goverde 2005)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	very serious[3]	none	24/85 (28.2%)	27/86 (31.4%)	RR 0.9 (0.57 to 1.43)	31 fewer per 1000 (from 135 fewer to 135 more)	VERY LOW
Pregnancy rates - Multiple pregnancies											
2(Goverde 2005, Guzick 1999)	RCT	serious[1]	no serious inconsistency[4]	no serious indirectness[7]	no serious imprecision[8]	none	14/316 (4.4%)	1/320 (0.31%)	RR 9.78 (1.84 to 51.91)	27 more per 1000 (from 3 more to 159 more)	MODERATE
Pregnancy related adverse events - Preterm birth											
1(Guzick 1999)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	serious[6]	none	9/231 (3.9%)	2/234 (0.85%)	RR 4.56 (1 to 20.87)	30 more per 1000 (from 0 more to 170 more)	LOW
Pregnancy related adverse events - Stillbirth											
1(Guzick 1999)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	very serious[3]	none	0/231 (0%)	1/234 (0.43%)	RR 0.34 (0.01 to 8.25)	3 fewer per 1000 (from 4 fewer to 31 more)	VERY LOW
Pregnancy related adverse events - Ectopic											
1(Guzick 1999)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	very serious[3]	none	4/231 (1.7%)	2/234 (0.85%)	RR 2.02 (0.37 to 10.95)	9 more per 1000 (from 5 fewer to	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with stimulation	IUI without stimulation	Relative (95% CI)	Absolute	
										85 more)	
Pregnancy related adverse events - Miscarriage											
1(Guzick 1999)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	no serious imprecision[8]	none	22/231 (9.5%)	6/234 (2.6%)	RR 3.71 (1.57 to 8.99)	69 more per 1000 (from 15 more to 205 more)	MODERATE
Pregnancy related adverse events - Induced abortion											
1(Guzick 1999)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	very serious[3]	none	0/231 (0%)	1/234 (0.43%)	RR 0.34 (0.01 to 8.25)	3 fewer per 1000 (from 4 fewer to 31 more)	VERY LOW
Pregnancy related adverse events - Total											
1(Guzick 1999)	RCT	serious[1]	no serious inconsistency[2]	no serious indirectness[7]	no serious imprecision	none	35/231 (15.2%)	12/234 (5.1%)	RR 2.95 (1.57 to 5.55)	100 more per 1000 (from 29 more to 233 more)	MODERATE

1 Evidence was downgraded by 1 as blinding was not reported.
2 Inconsistency not applicable as no meta-analysis was conducted (outcome is from a single study).
3 Evidence was downgraded by 2 as 95% CIs crossed two MIDs.
4 No serious inconsistency as heterogeneity measure (I squared) < 50%.
5 Evidence was downgraded by 1 as the outcome 'live birth' is indirect for 'live singleton birth'.
6 Evidence was downgraded by 1 as 95% CIs crossed one MID.
7 No serious indirectness as population, intervention and outcome is in agreement with review protocol.
8 No serious imprecision as 95% CIs do not cross MIDs.

Appendix I: Forest plots

I.1 IUI without ovarian stimulation versus expectant management

Figure 1: Live births, 6 months treatment duration

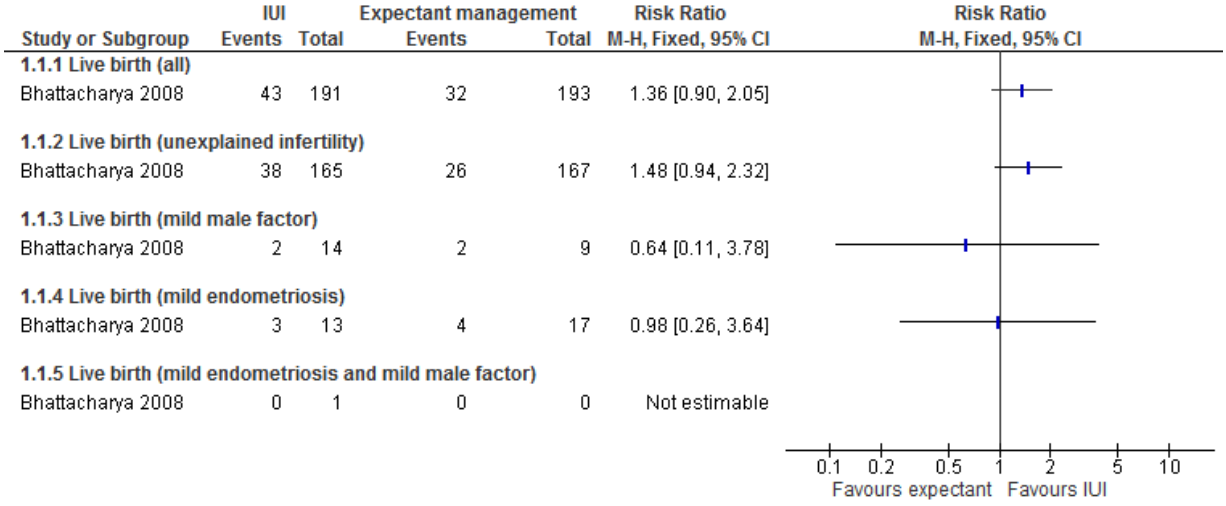


Figure 2: Pregnancy rate, 6 months treatment duration

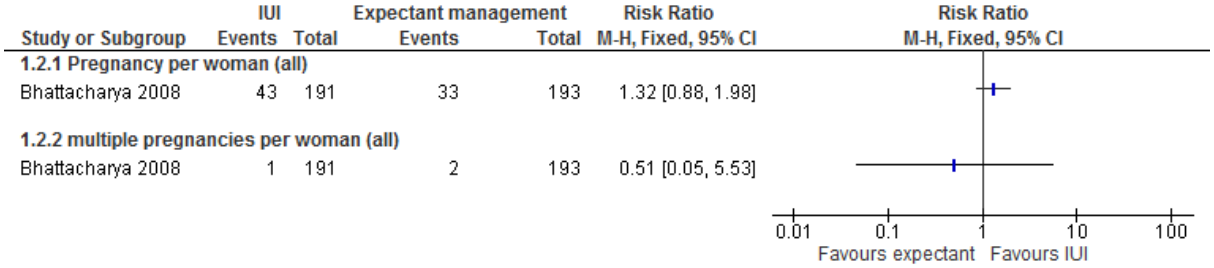


Figure 3: Pregnancy related adverse events, 6 months treatment duration

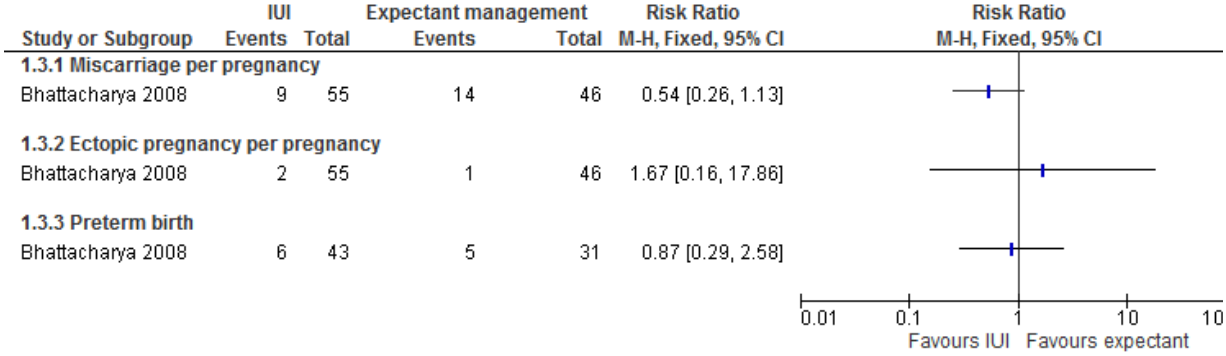


Figure 4: Patient related adverse events, 6 months treatment duration

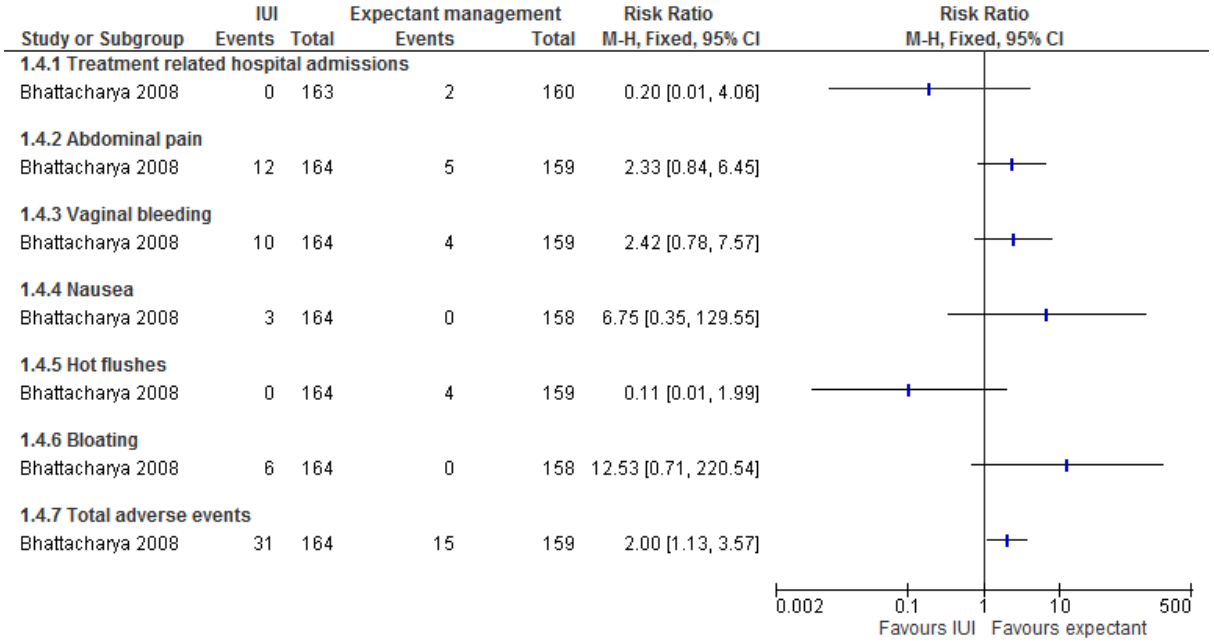


Figure 5: Patient satisfaction, 6 months treatment duration

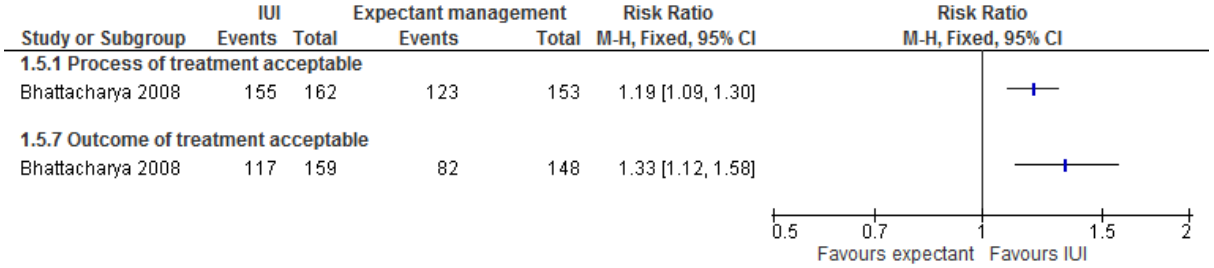


Figure 6: Anxiety, 6 months treatment duration

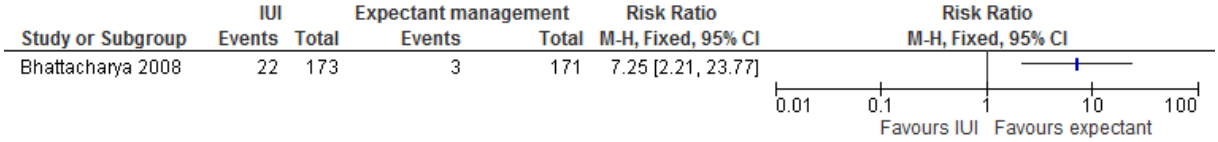
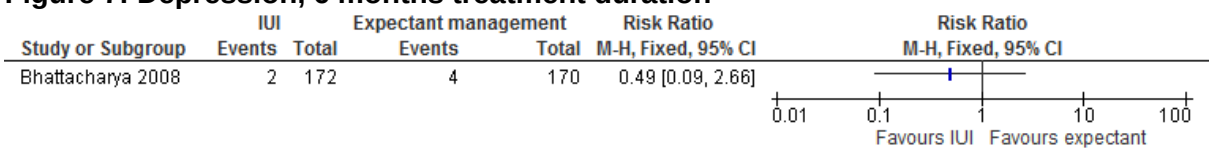


Figure 7: Depression, 6 months treatment duration



I.2 IUI with ovarian stimulation versus expectant management

Figure 8: Live births, up to 4 cycles

Study or Subgroup	IUI + stimulation Events	Total	Expectant management Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Live births (determined by interview, cumulative number after up to 4 cycles)					
Tummon 1997	14	53	4	50	3.30 [1.16, 9.36]
2.1.2 Live singleton births (number of live births - multiple births)					
Tummon 1997	11	53	4	50	2.59 [0.88, 7.62]
2.1.4 Live births					
Streures 2006	26	127	30	126	0.86 [0.54, 1.37]

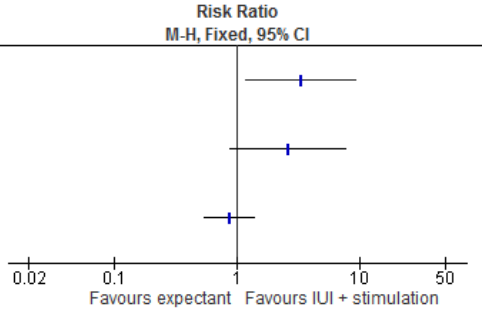


Figure 9: Multiple births, up to 4 cycles

Study or Subgroup	IUI + stimulation Events	Total	Expectant management Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.2.3 Live multiple births (determined by interview, cumulative number after up to 4 cycles)					
Tummon 1997	3	53	0	50	6.61 [0.35, 124.85]

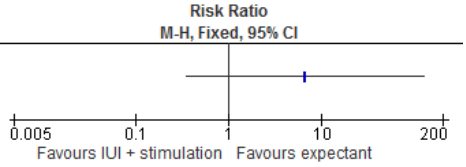


Figure 10: Ovarian hyperstimulation syndrome, up to 4 cycles

Study or Subgroup	IUI + stimulation Events	Total	Expectant management Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tummon 1997	0	53	0	50		Not estimable
Total (95% CI)		**53**		**50**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

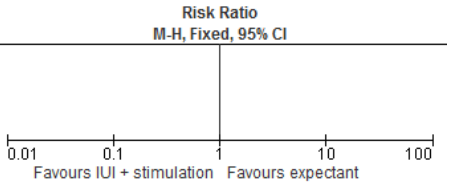


Figure 11: Pregnancy rate, 6 months treatment duration

Study or Subgroup	IUI + stimulation Events	Total	Expectant management Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Pregnancy (clinical/ongoing), 6 months					
Streures 2006	29	127	34	126	0.85 [0.55, 1.30]

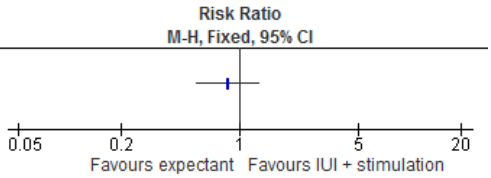


Figure 12: Pregnancy rate (multiple pregnancy), 6 months treatment duration

Study or Subgroup	IUI + stimulation Events	Total	Expectant management Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.4.3 Multiple pregnancies, 6 months					
Streures 2006	2	127	1	126	1.98 [0.18, 21.61]

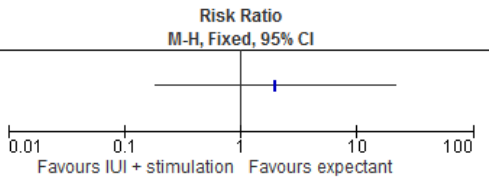
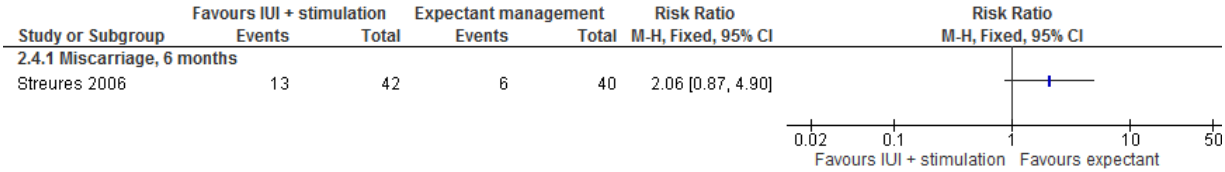


Figure 13: Pregnancy related adverse events, 6 months treatment duration and 3 year follow-up



I.3 IUI with ovarian stimulation versus IUI without ovarian stimulation

Figure 14: Live birth, up to or including 4 cycles

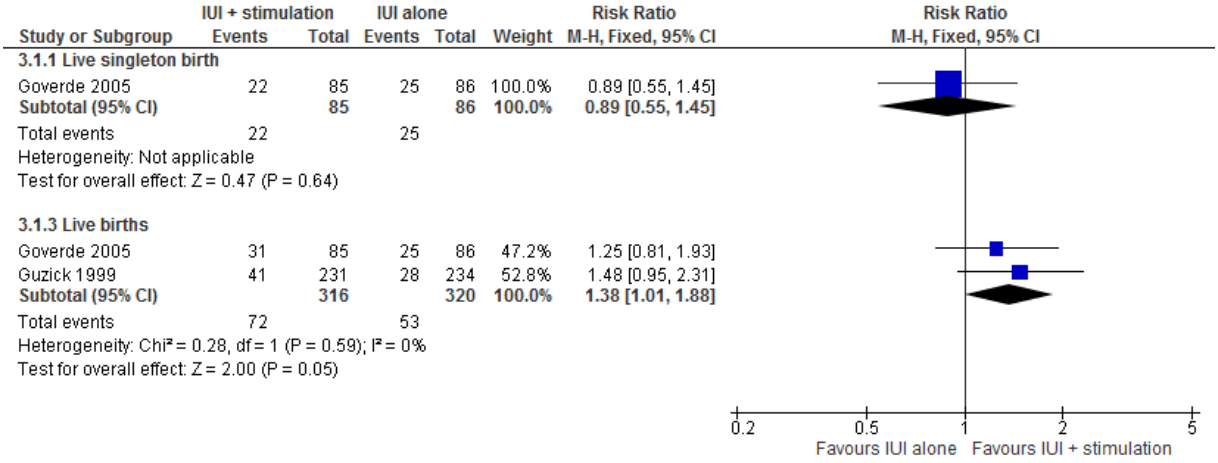


Figure 15: Pregnancy rates

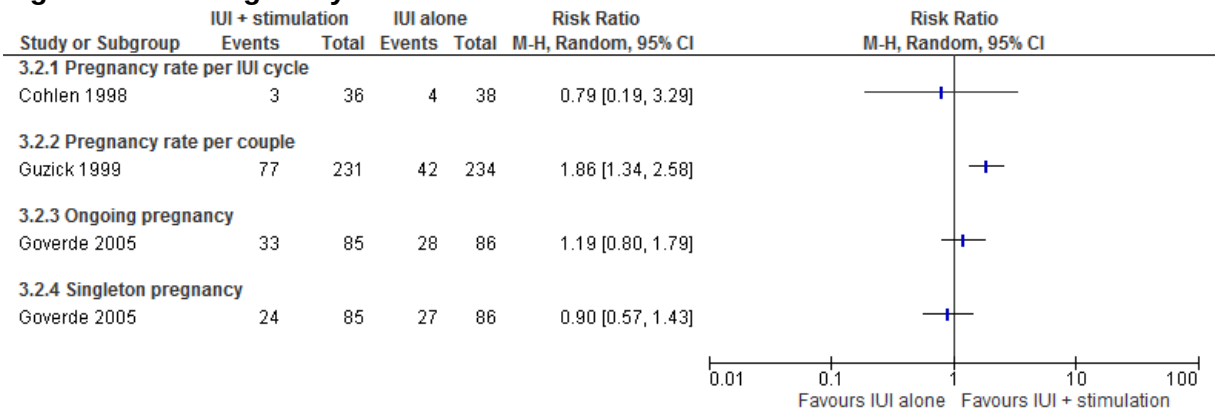


Figure 16: Pregnancy rates (multiple pregnancy rate)

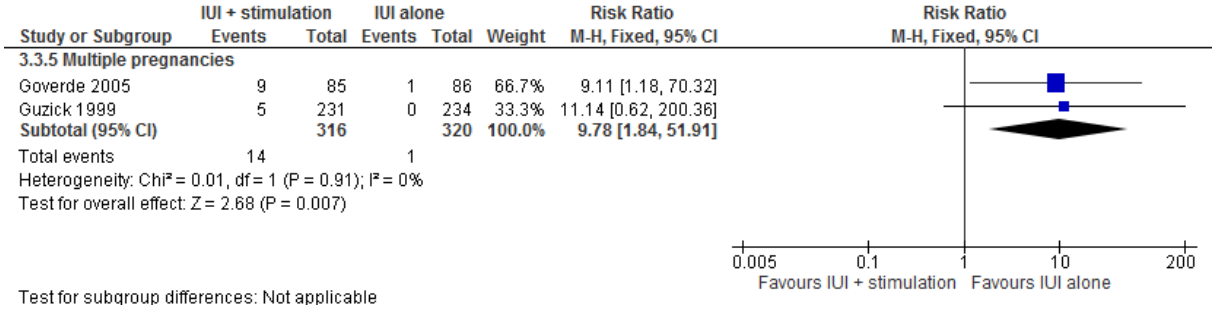
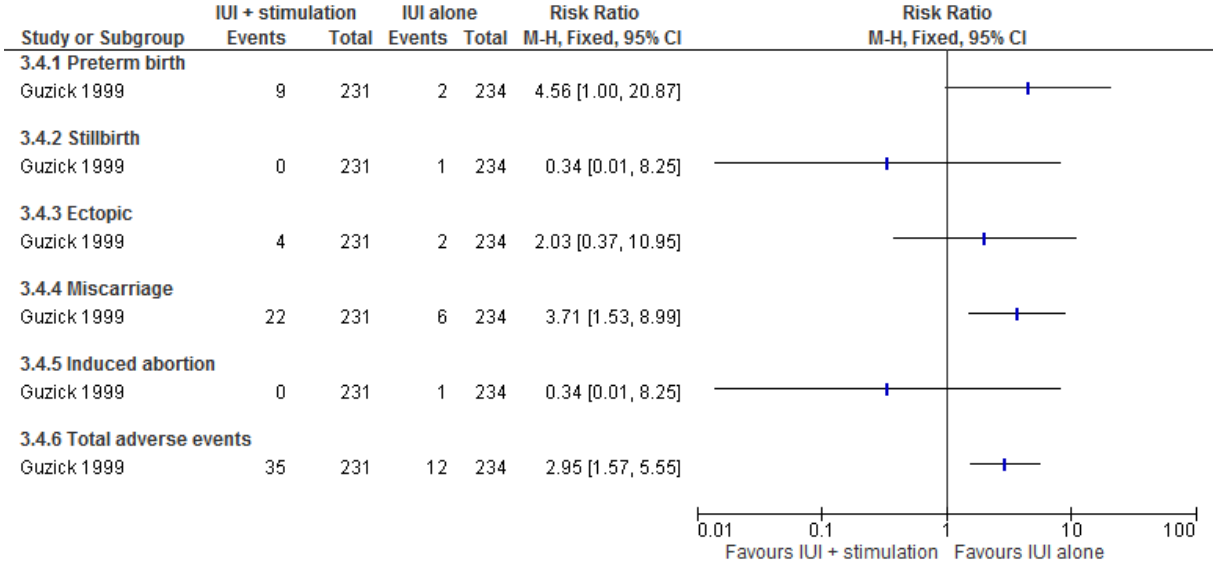


Figure 17: Pregnancy related adverse events, up to 4 cycles



Appendix J: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in table 10 (numbers marked with A reflect the original search strategy and are date limited form the last searches done as part of the guideline in 2011. Those marked with B include terms for endometriosis (missing from the former) and are not date limited). The search strategy is shown in table 11. The same strategy was translated for the other databases listed.

Table 15: Economic search summary

Database	Date searched	Version/files	Number retrieved
MEDLINE (Ovid)	17/12/2015	1946 to November wk 3 2015	A 45 B 24

Database	Date searched	Version/files	Number retrieved
MEDLINE in Process (Ovid)	17/12/2015	December 10 2015	A 12 B 1
Embase (Ovid)	17/12/2015	1974 to 2015 December 16	A 79 B 35
NHS Economic Evaluation Database (NHS EED) (legacy database)	16/12/2015	2 of 4 April 2015	A 6 B 0
Health Technology Assessment (HTA Database)	16/12/2015	4 of 4 October 2015	A 0 B 1

Table 16: Economic search strategy

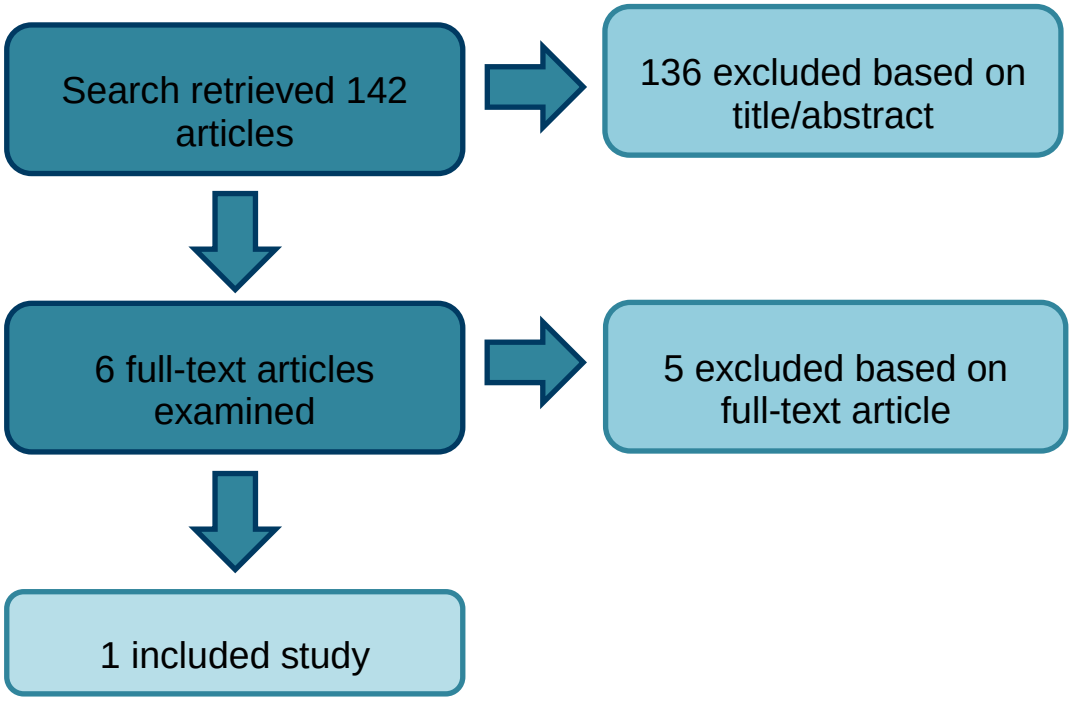
Database: Medline
Strategy used: Database: Ovid MEDLINE(R) <1946 to November Week 3 2015> Search strategy: 1 (fertil* or steril* or infertil* or subfertil* or sub-fertil* or fecund* or subfecund* or sub-fecund* or assist* reproduc*).tw. (216988) 2 exp Infertility/ (56305) 3 Infertility, Female/ (24939) 4 Infertility, Male/ (19577) 5 Anovulation/ (2038) 6 anovulat*.tw. (4609) 7 (oligo-ovulation or "oligo ovulation" or oligoovulat*).tw. (89) 8 Endometriosis/ (18136) 9 endometrio*.tw. (21349) 10 or/1-9 (255103) 11 exp Insemination, Artificial/ (10450) 12 ((artificial* or homologous or heterologous) adj4 inseminat*).tw. (5688) 13 (iui or siui).tw. (1240) 14 ((intrauterine or intra-uterine) adj inseminat*).tw. (1984) 15 or/11-14 (13231) 16 10 and 15 (6758) 17 Economics/ (27226) 18 exp "Costs and Cost Analysis"/ (196001) 19 Economics, Dental/ (1888) 20 exp Economics, Hospital/ (20954) 21 exp Economics, Medical/ (14109) 22 Economics, Nursing/ (3971) 23 Economics, Pharmaceutical/ (2651) 24 Budgets/ (10260) 25 exp Models, Economic/ (11339) 26 Markov Chains/ (11136) 27 Monte Carlo Method/ (22332) 28 Decision Trees/ (9466) 29 econom$.tw. (172061) 30 cba.tw. (9034) 31 cea.tw. (17413) 32 cua.tw. (830) 33 markov$.tw. (13106)

Database: Medline

34 (monte adj carlo).tw. (23053)
35 (decision adj3 (tree$ or analys$)).tw. (9287)
36 (cost or costs or costing$ or costly or costed).tw. (337974)
37 (price$ or pricing$).tw. (25166)
38 budget$.tw. (18575)
39 expenditure$.tw. (38080)
40 (value adj3 (money or monetary)).tw. (1458)
41 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2994)
42 or/17-41 (713050)
43 "Quality of Life"/ (134305)
44 quality of life.tw. (156308)
45 "Value of Life"/ (5534)
46 Quality-Adjusted Life Years/ (8172)
47 quality adjusted life.tw. (6908)
48 (qaly$ or qald$ or qale$ or qtime$).tw. (5640)
49 disability adjusted life.tw. (1468)
50 daly$.tw. (1408)
51 Health Status Indicators/ (21273)
52 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16967)
53 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1077)
54 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3059)
55 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
56 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (344)
57 (euroqol or euro qol or eq5d or eq 5d).tw. (4612)
58 (qol or hql or hqol or hrqol).tw. (28232)
59 (hye or hyes).tw. (60)
60 health$ year$ equivalent$.tw. (38)
61 utilit$.tw. (124842)
62 (hui or hui1 or hui2 or hui3).tw. (945)
63 disutili$.tw. (243)
64 rosser.tw. (71)
65 quality of wellbeing.tw. (5)
66 quality of well-being.tw. (349)
67 qwb.tw. (179)
68 willingness to pay.tw. (2573)
69 standard gamble$.tw. (698)
70 time trade off.tw. (807)
71 time tradeoff.tw. (222)
72 tto.tw. (650)
73 or/43-72 (355595)
74 42 or 73 (1020218)
75 16 and 74 (486)
76 animals/ not humans/ (4060674)
77 75 not 76 (343)
78 limit 77 to english language (303)
79 limit 78 to ed=20111120-20151217 (45)
80 8 or 9 (24913)

Database: Medline	
81	15 and 80 (246)
82	74 and 81 (32)
83	82 not 79 (28)
84	limit 83 to english language (24)

Appendix K: Economic review flowchart



Appendix L:Economic excluded studies

Reference	Reason for exclusion
Bevan,R.K., Winston,R.M.L., Souter,V., Penney,G., Donaldson,C., Ryan,M., Assessing the costs of assisted reproductive techniques, British Journal of Obstetrics and Gynaecology 1996 103 p.1049-1050	Not applicable: Incorrect study type (comment article).
Custers,I.M., van Rumste,M.M., van der Steeg,J.W., van,Wely M., Hompes,P.G., Bossuyt,P., Broekmans,F.J., Renckens,C.N., Eijkemans,M.J., van Dessel,T.J., van,der,V, Mol,B.W., Steures,P., Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment, Human Reproduction 2012 27 p.444-450	Not applicable: Incorrect interventions (EM followed by no treatment, IUI or IVF followed by IVF vs. IUI-COS followed by no treatment, IUI or IVF followed by IVF). Only costs per ongoing pregnancy were presented. The applied discount rate (5%) was not in line with the NICE reference case. Dutch costing data were used, which have limited applicability to the UK NHS context.
Guzick,D.S., Sullivan,M.W., Adamson,G.D., Cedars,M.I., Falk,R.J., Peterson,E.P., Steinkampf,M.P., Efficacy of treatment for unexplained infertility, Fertility & Sterility 1998 70 p.207-213	Not applicable: Only costs per incremental pregnancy were presented. US costing data were used, which are inapplicable to the UK NHS context (additionally costing data were sourced from unrepresentative local communities).
Philips,Z., Barraza-Llorens,M., Posnett,J., Evaluation of the relative cost-effectiveness of treatments for infertility in the UK, Human Reproduction 2000 15 p.95-106	Not applicable: Incorrect comparator (IVF instead of expectant management) in the unexplained infertility group.
Romundstad,L.B., Opdahl,S., Pinborg,A., Which treatment option for couples with unexplained or mild male subfertility? Intrauterine insemination looks like the best first choice, British Medical Journal (Online) 2015 350 p.-	Not applicable: Incorrect study type (editorial).

Acronyms
EM: Expectant Management; IUI: Intrauterine Insemination; IUI-COS: Intrauterine Insemination and Controlled Ovarian Stimulation; IVF: In Vitro Fertilisation

Appendix M: Full economic evidence tables

These are the full evidence tables for included economic studies.

Table 17: Full economic evidence tables

Bibliographic reference	**Wordsworth,S., Buchanan,J., Mollison,J., Harrild,K., Robertson,L., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Bhattacharya,S., Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective?, Human Reproduction 2011 Feb;26(2):369-75**
Evaluation design	

Interventions	Intrauterine insemination (women randomised to IUI monitored their mid-morning urinary luteinizing hormone concentrations from Day 12 of their cycle using Clearview. A single insemination was performed 20-30 h after detecting an endogenous surge. Semen was prepared with a swim-up technique with Puresperm density gradient followed by resuspension in a sperm butter. A maximum of 0.5 ml suspension of processed spermatozoa was introduced into the uterine cavity through the cervix with a 10 cm IUI catheter)
Comparators	Expectant management (couples were only given general advice for regular intercourse) Third arm: Clomifene citrate (oral dose of 50 mg between Day 2 and 6 of each treatment cycle)
Base-line cohort characteristics	Women attending fertility clinics across five hospitals in Scotland participating in the SUIT trial. Inclusion criteria included infertility for over two years, confirmed ovulation, patent fallopian tubes and motile sperm
Type of Analysis	Within-trial analysis based on cost and resource use data collected alongside the SUIT clinical trial over the 6 month follow-up period per patient
Structure	Not applicable
Cycle length	Not applicable
Time horizon	6 months
Perspective	UK National Health Service
Country	United Kingdom
Currency unit	£
Cost year	2006
Discounting	Not applicable (equipment costs were calculated using equivalent annual costing – a 6% discount rate was used as the costing was conducted before 3.5% advice, but it was varied in a sensitivity analysis)

Bibliographic reference	**Wordsworth,S., Buchanan,J., Mollison,J., Harrild,K., Robertson,L., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Bhattacharya,S., Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective?, Human Reproduction 2011 Feb;26(2):369-75**	
	Other comments	For each patient, the overall cost of treatment was calculated by multiplying the treatment cost per cycle for the relevant hospital by the number of cycles of treatment undertaken over the course of the 6 month follow-up period per patient. This treatment cost was supplemented by data on the incidence of adverse events (such as dilatation and curettage), collected during the trial. National unit costs (adjusted for length of stay) were attached to these admissions (ISD Scotland, 2006). Costs of antenatal and post-natal care were not included as they were assumed to be the same across the interventions).
Results		
	Comparison	EM vs. IUI
	Incremental cost	£319.39
	Incremental effects	0.06 live births
	Incremental cost effectiveness ratio	£5603.88 (-12204 to 2227) per additional live birth
	Conclusion	The ICER for IUI versus EM was £5604 (-12204 to 2227), with CC always being dominated. In terms of commonly used thresholds, these results suggest that IUI could only be considered cost-effective if EM were not an option. A threshold analysis indicated that the live birth rate for IUI would have to be 27% before it could be considered to be a cost-effective option, given the cost of treatment.
Data sources		
	Base-line data	Not applicable (within-trial comparison of 3 groups)
	Effectiveness data	The SUIT effectiveness results were used in the economic evaluation. The live birth rates (not adjusted for loss to follow-up) for EM, CC and IUI were 32 of 193, 26 of 194 and 43 of 193, respectively.
	Cost data	Cost and resource use data for CC and IUI were collected using questionnaires in the five hospitals for staff, consumables, equipment and overheads. Staff costs were calculated by estimating the amount of time staff spent on the interventions, with local unit costs attached to these times. The mid-points of salary scales were used and national insurance and superannuation added. Consumables were measured by estimating the required amount for a typical patient and local unit costs were applied. Equipment costs were calculated using equivalent annual costing and a 6% discount rate. National overhead information was applied (ISD Scotland, 2006). The above data were combined and used to calculate the mean unit cost per single treatment cycle. The overall mean (SD) costs of

Bibliographic reference	**Wordsworth,S., Buchanan,J., Mollison,J., Harrild,K., Robertson,L., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Bhattacharya,S., Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective?, Human Reproduction 2011 Feb;26(2):369-75**

	treatment (including costs of adverse events – four patients (2 EM, 2 CC) required hospitalization for adverse events) for EM, CC and IUI were £12 (£117), £350 (£220) and £331 (£222), respectively.
Utility data	Not applicable (QALYs not reported)

Uncertainty

One-way sensitivity analysis	The varied parameters included CC drug costs (50% increase and 50% decrease), the percentage value used to calculate overheads (zero overheads and a 100% increase in overheads), staff costs (50% increase) and the discount rate for capital items (3.5% instead of 6%). CC was still dominated regardless of any cost changes. The ICER for IUI versus EM treatment was highest when staff costs for IUI were increased by 50% at £6618. When overheads were reduced to zero, this ICER was also reduced to £5037. Different discount rates had little effect.
Probabilistic sensitivity analysis	Cost-effectiveness acceptability curves were presented to illustrate uncertainty around the ICER estimates. If the cost-effectiveness ceiling ratio is £30 000 per an additional live birth, EM has approximately a 15% probability of being the most cost-effective intervention, while IUI has approximately an 80% chance. If the ceiling ratio is £20 000 per an additional live birth, EM has 20% probability of being cost-effective, and IUI has approximately an 80% probability (read off graph). But if decision makers are willing to pay £5000 per an additional live birth, it is EM which has an 80% probability of being the most cost-effective intervention, while IUI has approximately a 30% chance (read off graph). The results may seem counter-intuitive, but it needs to be taken into account that as the ceiling ration increases, the fact that IUI costs significantly more than EM becomes less important, because there is a greater willingness to accept an increase in cost for a given increase in effectiveness. So, differences in effectiveness, however small, drive the probability of finding a particular intervention the most cost-effective option within a group of interventions.

Bibliographic reference	**Wordsworth,S., Buchanan,J., Mollison,J., Harrild,K., Robertson,L., Tay,C., Harrold,A., McQueen,D., Lyall,H., Johnston,L., Burrage,J., Grossett,S., Walton,H., Lynch,J., Johnstone,A., Kini,S., Raja,A., Templeton,A., Bhattacharya,S., Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective?, Human Reproduction 2011 Feb;26(2):369-75**
Applicability	**Partially applicable** Population consisted of people with unexplained infertility (mild endometriosis or 'mild' male factor infertility were not mentioned). The study was carried out in Scotland, which may limit its generalizability. Most importantly, no Quality Adjusted Life Years (QALYs), which is the preferred outcome measure by NICE for economic analyses, were estimated and therefore it is difficult to make judgements on the cost effectiveness of the intervention using the NICE cost effectiveness threshold. Costs data used are unlikely to accurately represent costs currently experienced in 2016.
Limitations	**Very serious limitations** The economic study is characterised by very serious limitations, as it was conducted alongside an RCT, and therefore had a short time horizon of 6 months. QALYs were not included as outcomes. Number of Scottish clinics participating in the trial was limited, and it is uncertain whether resource and costing data collected are representative of the UK as a whole. There were quite significant differences between centres when it comes to costs and resource use. **Conflicts** Nil. The study was funded by the Chief Scientist Office of the Scottish Executive Health Department.

Acronyms
EM: Expectant Management; IUI: Intrauterine Insemination; IUI-COS: Intrauterine Insemination and Controlled Ovarian Stimulation; IVF: In Vitro Fertilisation; SD: Standard Deviation; QALY: quality-adjusted life year