National Institute for Health and Care Excellence

Draft for consultation

Fertility problems: assessment and treatment

[K] Assisted reproduction techniques for people with unexplained fertility problems, mild endometriosis, and mild male factor fertility problems

NICE guideline NGXXX

Evidence reviews underpinning recommendations 1.8.2 and 1.8.3

September 2025

Draft for consultation

This evidence review was developed by NICE

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Assisted reproduction techniques for people with unexplained fertility problems, mild endometriosis, and mild male factor fertility problems

Review question

What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, in vitro fertilisation (IVF) and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Introduction

Fertility problems are defined as unexplained when pregnancy has not been achieved after 12 months of regular unprotected sexual intercourse or after 6 cycles of artificial insemination, despite no health-related impediment to fertility having been identified by standard investigations (including semen analysis, tubal patency tests, and assessment of ovulation). In this review, those with mild male factor fertility problems and with mild endometriosis were also included as this is in line with the research studies.

Clinical prediction models suggest that those with unexplained fertility problems have a cumulative ongoing pregnancy rate of 27% after 12 months of regular unprotected sexual intercourse (van Eekelen 2017). For this reason, expectant management (regular intercourse but no active intervention) is often recommended as an initial treatment option for those with unexplained fertility problems. However, other treatment options are also available and include ovarian stimulation (most commonly with a gonadotropin, and/or anti-oestrogen or aromatase inhibitor), intrauterine insemination (IUI) with or without ovarian stimulation, or in vitro fertilisation (IVF).

Randomised controlled trials (RCTs) have explored the most effective treatment for unexplained fertility problems. However, no 1 trial has included and compared all available treatment options, and this makes it difficult to make coherent and transparent recommendations about treatment from traditional pairwise meta-analyses that can only compare 1 intervention against another. For this reason, this review used network meta-analyses (NMAs) to compare all relevant treatment options for unexplained fertility problems within 1 network to inform treatment recommendations.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	People with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter
Intervention	• Ovarian stimulation using: ○ clomifene citrate ○ letrozole or anastrozole ○ gonadotropins ○ gonadotropin + clomifene citrate ○ gonadotropin + (letrozole or anastrozole) • Intrauterine insemination (IUI) without ovarian stimulation • Intrauterine insemination with ovarian stimulation (IUI-OS): ○ clomifene citrate + IUI ○ letrozole or anastrozole + IUI ○ gonadotropins + IUI ○ (gonadotropin + clomifene citrate) + IUI ○ (gonadotropin + (letrozole or anastrozole)) + IUI • IVF (without intracytoplasmic sperm injection [ICSI]) • Expectant management (including timed intercourse)
Comparison	Trials comparing at least 2 of the above interventions
Outcome	**Critical** • Live birth rate • Clinical pregnancy rate • Multiple gestation (primary safety outcome) **Important** • Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Ovarian Hyperstimulation Syndrome (OHSS)

ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; IVF: in vitro fertilisation; OHSS: ovarian hyperstimulation syndrome; OS: ovarian stimulation

For further details see the review protocol in appendix A.

Methods and process

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

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

Summary of methods

Evidence synthesis

Network meta-analysis (NMA) was the main method used to synthesise evidence included in this review. NMA was employed to assess the following outcomes:

- Live birth
- Clinical pregnancy
- Multiple gestation

Pairwise meta-analysis was undertaken to assess the following outcomes:

- Pregnancy loss
- Ovarian Hyperstimulation Syndrome (OHSS)

Interventions and prognosis

Interventions were categorised according to the assisted reproduction technique (ART) and comparisons that were of interest to the guideline committee. The committee agreed that comparisons between different gonadotropins or between aromatase inhibitors were not relevant, so gonadotropins were treated as a class, and letrozole and anastrozole were grouped together. However, the committee were interested in the comparison between clomifene citrate, gonadotropins and letrozole/anastrozole and ovarian stimulation (OS) interventions and IUI + OS interventions were coded with these agents separated out.

Initially, grouping interventions according to the maximum number of cycles that were offered (1 cycle, 2-3 cycles, and ≥4 cycles) was explored. However, the results of this analysis were implausible, as higher rates of live birth and pregnancy were observed for 2-3 cycles than for the higher number of cycles. Further investigation of these anomalous findings suggested that heterogeneity was being introduced by studies that restricted inclusion criteria to those with a poor prognosis. For the pairwise and NMAs, stratified analyses were conducted for studies with a 'mixed prognosis' population (studies that did not restrict inclusion based on prognosis) and a 'poor prognosis' population (studies that restricted inclusion based on: prediction score using the Hunault prediction model [Hunault 2004] of natural conception leading to livebirth in the next year <30%; 30-40% chance of a spontaneous ongoing pregnancy in the next 12 months; female age 38-42 years). In order for the networks to remain connected, distinction based on the number of cycles was not used. IVF interventions that included only fresh cycles and those that included fresh and frozen cycles were combined into a single IVF class.

NMA models

Following appropriate tests of fit, either random effects or fixed effects models were used for the 3 outcomes examined in the NMA. Random effects models assume that the true effect can vary across studies as a result of differences that exist amongst studies whereas fixed effects models assume that the same true effect size applies to all studies. NMA assumes consistency of direct and indirect effects across the network, which was assessed using inconsistency checks.

Presentation of the NMA results

For critical outcomes (live birth, clinical pregnancy, and multiple gestation), results of the NMAs are presented as odds ratios (ORs) and log-odds ratios (LORs), with 95% Credible Intervals (CrI), for each intervention compared with expectant management, which was selected as the reference treatment. Results are provided for the base-case analysis of the full dataset as well as for populations with a 'mixed' and 'poor' prognosis.

Intervention effect estimates were used to calculate intervention rankings, reported as median rank with 95% credible interval, and the probability that each intervention is the most effective in the network. Note however, that ranking probabilities are unreliable when effect estimates are uncertain, with wide credibility intervals.

Threshold analysis was undertaken to test the robustness of treatment recommendations to potential biases or sampling variation in the included evidence.

Further detail on NMA methods and model fit statistics are reported in appendix L. The results of a threshold analysis are provided in appendix M and an inconsistency check report is available in appendix N.

Presentation of the pairwise comparisons results

For pairwise comparisons for important (but not critical) outcomes, meta-analyses were conducted to combine results from similar studies (see the methods document - supplement 1: methods).

Effectiveness evidence

Included studies

Thirty-eight randomised controlled trials (RCTs) were included for this review (Agarwal 2004; Akbari 2012; Akbary-Asbagh 2007; Al-Fozan 2004; Al-Inany 2010; Bensdorp 2015; Bhattacharya 2008; Custers 2011; Danhof 2018; Dankert 2007; Davar 2006a; Davar 2006b; Diamond 2015; El Helw 2002; Elzeiny 2014; Erdem 2015; Farquhar 2018; Fatemi 2003; Fouda 2011; Galal 2015; George 2006; Goldman 2014; Goverde 2000; Huang 2021; Ibrahim 2012; Jamal 2005; Kaur 2019; Malhotra 2012; Nada 2016; Nayar 2008; Ozmen 2005; Sammour 2001; Steures 2006; Taravat 2011; Thyagaraju 2022; Wessel 2022; Wu 2007; Zadehmodares 2012).

Thirty-one RCTs included a mixed prognosis population (Agarwal 2004; Akbari 2012; Akbary-Asbagh 2007; Al-Fozan 2004; Al-Inany 2010; Bhattacharya 2008; Dankert 2007; Davar 2006a; Davar 2006b; Diamond 2015; El Helw 2002; Elzeiny 2014; Erdem 2015; Fatemi 2003; Fouda 2011; Galal 2015; George 2006; Goverde 2000; Huang 2021; Ibrahim 2012; Jamal 2005; Kaur 2019; Malhotra 2012; Nada 2016; Nayar 2008; Ozmen 2005; Sammour 2001; Taravat 2011; Thyagaraju 2022; Wu 2007; Zadehmodares 2012).

Seven RCTs included a poor prognosis population, defined as a prediction score using the Hunault prediction model of <30% for spontaneous conception in the next year (Bensdorp 2015; Custers 2011; Danhof 2018; Farquhar 2018; Wessel 2022), a prediction score using the Hunault prediction model of 30-40% for spontaneous conception in the next year (Steures 2006), or female age 38-42 years (Goldman 2014).

The included studies are summarised in Table 2.

For the live birth NMA, the network of evidence (and the respective NMA) included 16 RCTs, 9 interventions, and 4,755 participants.

For the clinical pregnancy NMA, the network of evidence (and the respective NMA) included 36 RCTs,12 interventions, and 7,406 participants.

For the multiple gestation NMA, the network of evidence (and the respective NMA) included 20 RCTs, 12 interventions, and 1,553 participants.

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Interventions	Outcomes	Comments
Agarwal 2004 RCT India	N randomised: 140 Female age in years, mean (SD): 29.1 (4.4) Duration of subfertility in years, mean (SD): 4.9 (3.1) Primary infertility (%): 72 Mild endometriosis (%): NR Mild male factor (%): NR	• Clomifene citrate (n=70) • IUI + clomifene citrate (n=70) Number of cycles of treatment offered: 6 Mean number of cycles undergone: 4.9 Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Paper reported results based on number with complete follow-up data
Akbari 2012 RCT Iran	N randomised: 160 Female age in years, mean (SD): 28.5 (4.6) Duration of subfertility in years, mean (SD): 5.7 (3.3) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI with gonadotropin + clomifene citrate (n=80) • IUI with gonadotropin + letrozole/anastrozole (n=80) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** • Pregnancy loss	Mixed prognosis Gonadotropin: human menopausal gonadotropin (hMG) Aromatase inhibitor: letrozole
Akbary-Asbagh 2007 RCT Iran	N randomised: 150 Female age in years, mean (SD): 27.5 (3.8) Duration of subfertility in	• IUI + gonadotropin (n=46) • IUI with gonadotropin + clomifene citrate (n=52) • IUI with gonadotropin + letrozole/anastrozole (n=52)	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Paper reported results based on number with complete follow-up data Gonadotropin: human

Study	Population	Interventions	Outcomes	Comments
	years, mean (SD): 4.2 (2.3) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR		menopausal gonadotropin (hMG) Aromatase inhibitor: letrozole
Al-Fozan 2004 RCT Canada	N randomised: 154 Female age in years, mean (SD): 31.1 (4.4) Duration of subfertility in years, mean (SD): 2.8 (2.3) Primary infertility (%): 66 Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=80) • IUI + letrozole/anastrozole (n=74) Number of cycles of treatment offered: NR Mean number of cycles undergone: 1.5 Duration of treatment (months): NR	**Critical:** • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss	Mixed prognosis Aromatase inhibitor: letrozole
Al-Inany 2010 RCT Egypt	N randomised: 230 Female age in years, mean (SD): 27.9 (3.9) Duration of subfertility in years, mean (SD): 2.8 (1.8) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): 48	• Gonadotropins + IUI (n=115) • (Gonadotropin + clomifene citrate) + IUI (n=115) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy • Multiple gestation **Important:** None	Mixed prognosis Paper reported results based on number with complete follow-up data Gonadotropin: human menopausal gonadotropin (hMG)

Study	Population	Interventions	Outcomes	Comments
Bensdorp 2015 RCT Netherlands	N randomised: 602 Female age in years, mean (SD): 33.3 (3.6) Duration of subfertility in years, mean (SD): NR Primary infertility (%): 76 Mild endometriosis (%): NR Mild male factor (%): 9	• IUI + clomifene citrate/gonadotropin (n=207) • IVF (n=201) • IVF modified natural cycle (n=194) Number of cycles of treatment offered: IUI + ovarian stimulation (OS): 6 IVF: 3 IVF modified cycle: 6 Mean number of cycles undergone: IUI + OS: 4 IVF: 1.5 IVF modified cycle: 3.3 Duration of treatment (months): 10	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulation Syndrome	Poor prognosis (defined as a prediction score using the Hunault prediction model of <30% for spontaneous conception in the next year) Participants followed up for 12 months after randomisation Gonadotropin (when used): follicle-stimulating hormone (FSH) IVF: fresh and frozen cycles
Bhattacharya 2008 RCT UK	N randomised: 580 Female age in years, mean (SD): 32.0 (3.5) Duration of subfertility in years, mean (SD): NR (median 30 months) Primary infertility (%): 71 Mild endometriosis (%): 7 Mild male factor (%): 6	• Clomifene citrate (n=194) • IUI (without OS) (n=193) • Expectant management (n=193) Number of cycles of treatment offered: 6 Mean number of cycles undergone: NR; medians 5 clomifene citrate; 4 IUI Duration of treatment (months): 6	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss	Mixed prognosis
Custers 2011 RCT Netherlands	N randomised: 116 Female age in years, mean (SD): 33.8 (2.9)	• IUI + gonadotropin (n=58) • IVF (n=58) Number of cycles of treatment offered: IUI + OS: 3 IVF: 1	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** None	Poor prognosis (defined as a prediction score using the Hunault prediction model of <30% for spontaneous conception in the next year)

Study	Population	Interventions	Outcomes	Comments
	Duration of subfertility in years, mean (SD): NR Primary infertility (%): 85 Mild endometriosis (%): NR Mild male factor (%): 9	Mean number of cycles undergone: IUI + OS: 2.7 Duration of treatment (months): 4		Gonadotropin: recombinant follicle-stimulating hormone (rFSH) IVF: fresh and frozen
Danhof 2018 RCT Netherlands	N randomised: 738 Female age in years, mean (SD): 33.1 (5.1) Duration of subfertility in years, mean (SD): NR (median 24 months) Primary infertility (%): 73 Mild endometriosis (%): NR Mild male factor (%): 4	• IUI + clomifene citrate (n=369) • IUI + gonadotropin (n=369) Number of cycles of treatment offered: 4 Mean number of cycles undergone: 3.2 Duration of treatment (months): 6	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss	Poor prognosis (defined as a prediction score using the Hunault prediction model of <30% for spontaneous conception in the next year) Gonadotropin: follicle-stimulating hormone (FSH)
Dankert 2007 RCT Netherlands	N randomised: 68 Female age in years, mean (SD): 31.3 (NR) Duration of subfertility in years, mean (SD): 2.8 (NR) Primary infertility (%): 100 Mild endometriosis (%): NR	• IUI + clomifene citrate (n=35) • IUI + gonadotropin (n=33) Number of cycles of treatment offered: 4 Mean number of cycles undergone: 2.8 Duration of treatment (months): NR	**Critical:** • Live birth **Important:** None	Mixed prognosis Paper reports results for unexplained subfertility subgroup and male factor subfertility subgroup but data only included for subgroup with unexplained subfertility (as severity of male factor subfertility unclear and diagnostic

Study	Population	Interventions	Outcomes	Comments
	Mild male factor (%): 0			groups randomised separately) Gonadotropin: recombinant follicle-stimulating hormone (rFSH)
Davar 2006a RCT Iran	N randomised: 95 Female age in years, mean (SD): 27.2 (3.8) Duration of subfertility in years, mean (SD): 5.6 (2.5) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): 29	• IUI with gonadotropin + clomifene citrate (n=53) • IUI with gonadotropin + letrozole/anastrozole (n=42) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulation Syndrome	Mixed prognosis Gonadotropin: follicle-stimulating hormone (FSH) Aromatase inhibitor: letrozole
Davar 2006b RCT Iran	N randomised: 115 Female age in years, mean (SD): 27.3 (3.7) Duration of subfertility in years, mean (SD): 5.8 (2.5) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): 28	• IUI with gonadotropin + clomifene citrate (n=55) • IUI with gonadotropin + letrozole/anastrozole (n=60) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy • Multiple gestation **Important:** • Ovarian Hyperstimulation Syndrome	Mixed prognosis Gonadotropin: follicle-stimulating hormone (FSH) Aromatase inhibitor: letrozole
Diamond 2015 RCT	N randomised: 900	• IUI + clomifene citrate (n=300)	**Critical:** • Live birth • Clinical pregnancy	Mixed prognosis Participants followed up to

Study	Population	Interventions	Outcomes	Comments
US	Female age in years, mean (SD): 32.2 (4.3) Duration of subfertility in years, mean (SD): 2.9 (2.1) Primary infertility (%): 80 Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + letrozole/anastrozole (n=299) • IUI + gonadotropin (n=301) Number of cycles of treatment offered: 4 Mean number of cycles undergone: 2.9 Duration of treatment (months): NR	• Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulation Syndrome	15 months (duration of their treatment and, if pregnant through 6 weeks post-delivery) Gonadotropin: follicle-stimulating hormone (FSH) Aromatase inhibitor: letrozole
El Helw 2002 RCT Egypt	N randomised: 53 Female age in years, mean (SD): NR Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=26) • IUI + letrozole/anastrozole (n=27) Number of cycles of treatment offered: 3 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Conference abstract but data extracted from Cantineau 2021 Aromatase inhibitor: letrozole
Elzeiny 2014 RCT Australia	N randomised: 44 Female age in years, mean (SD): 33.2 (4.0) Duration of subfertility in years, mean (SD): 3.2 (2.3) Primary infertility (%): 70	• IUI + gonadotropin (n=33) • IVF (n=11) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulation Syndrome	Mixed prognosis Randomisation only performed for women who had an ultrasound scan indicating that there would be 2-3 preovulatory follicles (>16 mm) at the time of hCG injection. Data only extracted for randomised participants

Study	Population	Interventions	Outcomes	Comments
	Mild endometriosis (%): NR Mild male factor (%): 33			Gonadotropin: recombinant follicle-stimulating hormone (rFSH) IVF: fresh and frozen cycles
Erdem 2015 RCT Turkey	N randomised: 219 Female age in years, mean (SD): 29.0 (5.2) Duration of subfertility in years, mean (SD): 3.4 (2.4) Primary infertility (%): 92 Mild endometriosis (%): NR Mild male factor (%): 17	• IUI + clomifene citrate (n=110) • IUI + gonadotropin (n=109) Number of cycles of treatment offered: 2 Mean number of cycles undergone: 1.5 Duration of treatment (months): 6	**Critical:** • Live birth • Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulation Syndrome	Mixed prognosis Gonadotropin: recombinant follicle-stimulating hormone (rFSH)
Farquhar 2018 RCT New Zealand	N randomised: 201 Female age in years, mean (SD): 34.0 (3.6) Duration of subfertility in years, mean (SD): 3.6 (NR) Primary infertility (%): 88 Mild endometriosis (%): 10 Mild male factor (%): NR	• IUI + clomifene citrate (n=101) • Expectant management (n=100) Number of cycles of treatment offered: 3 Mean number of cycles undergone: 2.5 Duration of treatment (months): 6	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss	Poor prognosis (defined as a prediction score using the Hunault prediction model of <30% for spontaneous conception in the next year) Participants in the IUI arm could receive letrozole or clomifene citrate, but only 7% of those in IUI arm received letrozole so intervention coded as IUI + clomifene citrate. Protocol suggests letrozole deviation from

Study	Population	Interventions	Outcomes	Comments
				intended intervention as only clomifene citrate in registered protocol
Fatemi 2003 RCT Belgium	N randomised: 15 Female age in years, mean (SD): NR Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=8) • IUI + letrozole/anastrozole (n=7) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Aromatase inhibitor: letrozole
Fouda 2011 RCT Egypt	N randomised: 214 Female age in years, mean (SD): 26.4 (3.4) Duration of subfertility in years, mean (SD): 3.6 (1.8) Primary infertility (%): 69 Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=107) • IUI + letrozole/anastrozole (n=107) Number of cycles of treatment offered: 3 Mean number of cycles undergone: 2 Duration of treatment (months): NR	**Critical:** • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulatio n Syndrome	Mixed prognosis Aromatase inhibitor: letrozole
Galal 2015 RCT Egypt	N randomised: 100 Female age in years, mean (SD): 26.1 (4.1)	• IUI + letrozole/anastrozole (n=50) • IUI + gonadotropin (n=50)	**Critical:** • Clinical pregnancy **Important:**	Mixed prognosis Conference abstract but data extracted

Study	Population	Interventions	Outcomes	Comments
	Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	None	from Cantineau 2021 Gonadotropin: human menopausal gonadotropin (hMG) Aromatase inhibitor: letrozole
George 2006 RCT India	N randomised: 140 Female age in years, mean (SD): NR Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• Clomifene citrate (n=70) • Expectant management (n=70) Number of cycles of treatment offered: 3 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss	Mixed prognosis Conference abstract but data extracted from Wang (2019) Ovulation trigger and placebo tablets included in the expectant management arm
Goldman 2014 RCT US	N randomised: 154 Female age in years, mean (SD): 40.3 (1.3) Duration of subfertility in years, mean (SD): NR Primary infertility (%): 27 Mild endometriosis (%): NR	• IUI + clomifene citrate (n=51) • IUI + gonadotropin (n=52) • IVF (n=51) Number of cycles of treatment offered: 2 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Live birth • Clinical pregnancy **Important:** • Pregnancy loss	Poor prognosis (defined as female age 38-42 years). Data only extracted for the first 2 treatment cycles (although a maximum of 6 cycles of treatment offered) as after 2 cycles the IUI arms received IVF if not pregnant

Study	Population	Interventions	Outcomes	Comments
	Mild male factor (%): NR			Gonadotropin: recombinant follicle-stimulating hormone (rFSH) IVF: fresh cycles only
Goverde 2000 RCT Netherlands	N randomised: 258 Female age in years, mean (SD): 31.8 (3.9) Duration of subfertility in years, mean (SD): 4.2 (2.2) Primary infertility (%): 87 Mild endometriosis (%): NR Mild male factor (%): 30	• IUI (without OS) (n=86) • IUI + gonadotropin (n=85) • IVF (n=87) Number of cycles of treatment offered: 6 Mean number of cycles undergone: 3.7 Duration of treatment (months): NR	**Critical:** • Live birth **Important:** None	Mixed prognosis Gonadotropin: follicle-stimulating hormone (FSH) IVF: fresh cycles only
Huang 2021 RCT China	N randomised: 100 Female age in years, mean (SD): 31.3 (3.2) Duration of subfertility in years, mean (SD): NR (median 36 months) Primary infertility (%): 69 Mild endometriosis (%): NR Mild male factor (%): 56	• IUI (without OS) (n=50) • IUI + letrozole/anastrozole (n=50) Number of cycles of treatment offered: 3 Mean number of cycles undergone: 2.4 Duration of treatment (months): 4	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss	Mixed prognosis Aromatase inhibitor: letrozole
Ibrahim 2012 RCT	N randomised: 270	• Clomifene citrate (n=134) • Letrozole/anastrozole (n=136)	**Critical:** • Clinical pregnancy	Mixed prognosis Paper reported results based on

Study	Population	Interventions	Outcomes	Comments
Egypt	Female age in years, mean (SD): 28.4 (3.2) Duration of subfertility in years, mean (SD): 5.0 (2.5) Primary infertility (%): 67 Mild endometriosis (%): NR Mild male factor (%): NR	Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	• Multiple gestation **Important:** • Ovarian Hyperstimulation Syndrome	number with complete follow-up data Aromatase inhibitor: letrozole
Jamal 2005 RCT Turkey	N randomised: 80 Female age in years, mean (SD): NR (range 20-35) Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + letrozole/anastrozole (n=40) • IUI + gonadotropin (n=40) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Conference abstract but data extracted from Cantineau 2021 Gonadotropin: human menopausal gonadotropin (hMG) Aromatase inhibitor: letrozole
Kaur 2019 RCT India	N randomised: 60 Female age in years, mean (SD): 30.0 (3.2) Duration of subfertility in years, mean (SD): 5.9 (3.1) Primary infertility (%): 69	• IUI + letrozole/anastrozole (n=30) • IUI with gonadotropin + letrozole/anastrozole (n=30) Number of cycles of treatment offered: NR Mean number of cycles undergone: 1.7 Duration of treatment (months): 3	**Critical:** • Clinical pregnancy • Multiple gestation **Important:** None	Mixed prognosis Paper reported results based on number with complete follow-up data Gonadotropin: human menopausal gonadotropin (hMG) Aromatase inhibitor: letrozole

Study	Population	Interventions	Outcomes	Comments
	Mild endometriosis (%): NR Mild male factor (%): NR			
Malhotra 2012 RCT India	N randomised: 68 Female age in years, mean (SD): NR Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + letrozole/anastrozole (n=37) • IUI with gonadotropin + letrozole/anastrozole (n=31) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** • None	Mixed prognosis Conference abstract but data extracted from Cantineau 2021 Gonadotropin: human menopausal gonadotropin (hMG) Aromatase inhibitor: letrozole
Nada 2016 RCT Egypt	N randomised: 622 Female age in years, mean (SD): 30.2 (5.4) Duration of subfertility in years, mean (SD): 5.5 (2.5) Primary infertility (%): 63 Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=311) • IUI + gonadotropin (n=311) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy • Multiple gestation **Important:** • Ovarian Hyperstimulation Syndrome	Mixed prognosis Paper reported results based on number with complete follow-up data Gonadotropin: human menopausal gonadotropin (hMG)
Nayar 2008 RCT India	N randomised: 145 Female age in years, mean (SD): NR	• IUI + clomifene citrate (n=75) • IUI + gonadotropin (n=70) Number of cycles of treatment offered: 1	**Critical:** • Clinical pregnancy • Multiple gestation **Important:**	Mixed prognosis Conference abstract but data extracted from Cantineau (2021)

Study	Population	Interventions	Outcomes	Comments
	Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	Mean number of cycles undergone: NR Duration of treatment (months): NR	• Ovarian Hyperstimulation Syndrome	Gonadotropin: recombinant follicle-stimulating hormone (rFSH)
Ozmen 2005 RCT Turkey	N randomised: 43 Female age in years, mean (SD): NR Duration of subfertility in years, mean (SD): NR Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=21) • IUI + letrozole/anastrozole (n=22) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Conference abstract but data extracted from Cantineau 2021 Aromatase inhibitor: letrozole
Sammour 2001 RCT Canada	N randomised: 49 Female age in years, mean (SD): 31.7 (NR) Duration of subfertility in years, mean (SD): 2.1 (NR) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=24) • IUI + letrozole/anastrozole (n=25) Number of cycles of treatment offered: 3 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Conference abstract but data extracted from Cantineau 2021 Aromatase inhibitor: letrozole

Study	Population	Interventions	Outcomes	Comments
Steures 2006 RCT Netherlands	N randomised: 253 Female age in years, mean (SD): 33.0 (3.3) Duration of subfertility in years, mean (SD): 2.0 (0.5) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + gonadotropin (n=127) • Expectant management (n=126) Number of cycles of treatment offered: 6 Mean number of cycles undergone: 3.5 Duration of treatment (months): 6	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss	Poor prognosis (defined as a prediction score using the Hunault prediction model of 30-40% for spontaneous conception in the next year) Gonadotropin: human menopausal gonadotropin (hMG) or follicle-stimulating hormone (FSH)
Taravat 2011 RCT Iran	N randomised: 55 Female age in years, mean (SD): 27.9 (4.1) Duration of subfertility in years, mean (SD): 4.6 (2.6) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI with gonadotropin + clomifene citrate (n=29) • IUI with gonadotropin + letrozole/anastrozole (n=26) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Gonadotropin: recombinant follicle-stimulating hormone (rFSH) Aromatase inhibitor: anastrozole
Thyagaraju 2022 RCT India	N randomised: 224 Female age in years, mean (SD): 29.2 (3.8) Duration of subfertility in years, mean (SD): 5.8 (3.1)	• IUI + clomifene citrate (n=112) • IUI + gonadotropin (n=112) Number of cycles of treatment offered: 3 Mean number of cycles undergone: 2.98 Duration of treatment	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulation Syndrome	Mixed prognosis Gonadotropin: human menopausal gonadotropin (hMG)

Study	Population	Interventions	Outcomes	Comments
	Primary infertility (%): 82 Mild endometriosis (%): NR Mild male factor (%): 28	(months): NR		
Wessel 2022 RCT Netherlands	N randomised: 178 Female age in years, mean (SD): 34.1 (4.1) Duration of subfertility in years, mean (SD): 1.8 (NR) Primary infertility (%): 68 Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate/gonadotropin (n=86) • Expectant management (n=92) Number of cycles of treatment offered: 6 Mean number of cycles undergone: 3.05 Duration of treatment (months): 6	**Critical:** • Live birth • Clinical pregnancy • Multiple gestation **Important:** None	Poor prognosis (defined as a prediction score using the Hunault prediction model of <30% for spontaneous conception in the next year) Trial stopped early because of a slow inclusion rate Gonadotropin (when used): NR
Wu 2007 RCT Taiwan	N randomised: 33 Female age in years, mean (SD): 32.9 (3.8) Duration of subfertility in years, mean (SD): 3.9 (2.6) Primary infertility (%): 67 Mild endometriosis (%): NR Mild male factor (%): NR	• IUI + clomifene citrate (n=19) • IUI + letrozole/anastrozole (n=14) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	**Critical:** • Clinical pregnancy **Important:** None	Mixed prognosis Aromatase inhibitor: anastrozole
Zadehmodarres 2012 RCT	N randomised: 106	• IUI with gonadotropin + clomifene citrate (n=53)	**Critical:** • Clinical pregnancy	Mixed prognosis Gonadotropin: recombinant

Study	Population	Interventions	Outcomes	Comments
Iran	Female age in years, mean (SD): 26.2 (4.1) Duration of subfertility in years, mean (SD): 5.0 (2.3) Primary infertility (%): NR Mild endometriosis (%): NR Mild male factor (%): NR	• IUI with gonadotropin + letrozole/anastrozole (n=53) Number of cycles of treatment offered: 1 Mean number of cycles undergone: NR Duration of treatment (months): NR	• Multiple gestation **Important:** • Pregnancy loss • Ovarian Hyperstimulation Syndrome	follicle-stimulating hormone (rFSH) Aromatase inhibitor: letrozole

hCG: human chorionic gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NR: not reported; OHSS: ovarian hyperstimulation syndrome; OS: ovarian stimulation; RCT: randomised controlled trial; SD: standard deviation

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

Summary of the evidence from the network meta-analysis

The full results of the NMAs with the best fitting model, either random or fixed effect, are presented below. The numbers of people treated each intervention for the three outcomes (clinical pregnancy, live birth and multiple birth) are shown in Table 3. Subsequently, for each outcome, we first present the evidence network plot and results (relative effects of each treatment versus expectant management) both in a forest-like plot and in tabulated form.

In each network plot presented below, the width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.

Table 3. Interventions and numbers of participants (pregnancies for multiple birth outcome) treated on NMAs of clinical pregnancy, live birth and multiple birth for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter

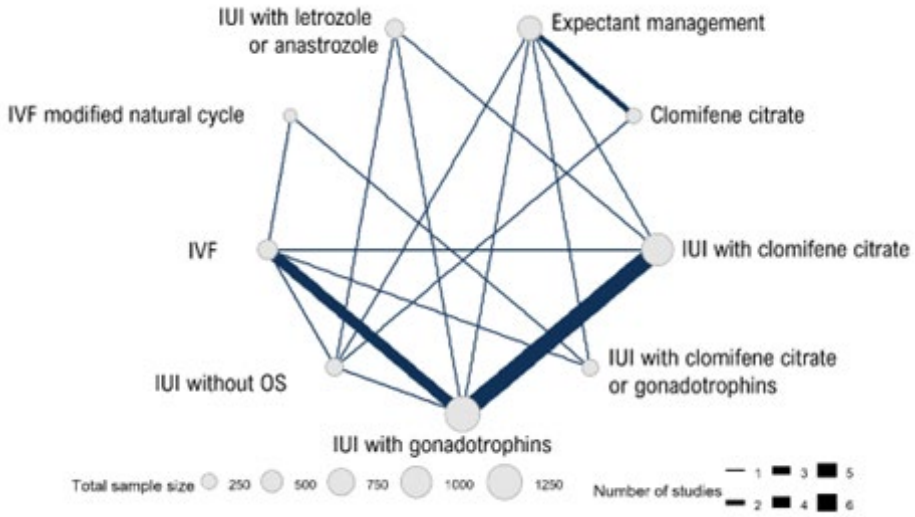
Intervention	Sub-category	Clinical pregnancy (n)			Live birth (n)			Multiple birth (n)	
		Full dataset	Mixed prognosis	Poor prognosis	Full dataset	Mixed prognosis	Poor prognosis	Full dataset	Poor prognosis
Expectant management		581	263	318	581	263	318	114	114
Clomiphene citrate		468	468	No data	264	264		57	
Clomiphene citrate + IUI		1784	1263	521	1078	557	521	312	312
Clomiphene citrate or gonadotropin + IUI		293	No data	293	293	No data	293	169	169
Gonadotropin + clomiphene citrate + IUI		437	437	No data	No data	No data	No data	27	No data
Gonadotropin + IUI		1793	1187	606	1279	673	606	385	385
Gonadotropin + anastrozole/letrozole + IUI		374	374	No data	No data	No data	No data	24	No data
IUI without OS		243	243	No data	329	329	No data	43	
IVF	modified natural cycle (fresh)	194	No data	194	194	No data	194	115	115
	All IVF excluding natural	321	11	310	408	98	310	154	154
Anastrozole/letrozole		136	136	No data	No data	No data	No data	30	No data
Anastrozole/letrozole + IUI		782	782	No data	349	349	No data	123	No data
TOTAL		**7,406**	**5,164**	**2,242**	**4,775**	**2,533**	**2,242**	**1,553**	**1,249**

Live Birth

Full dataset

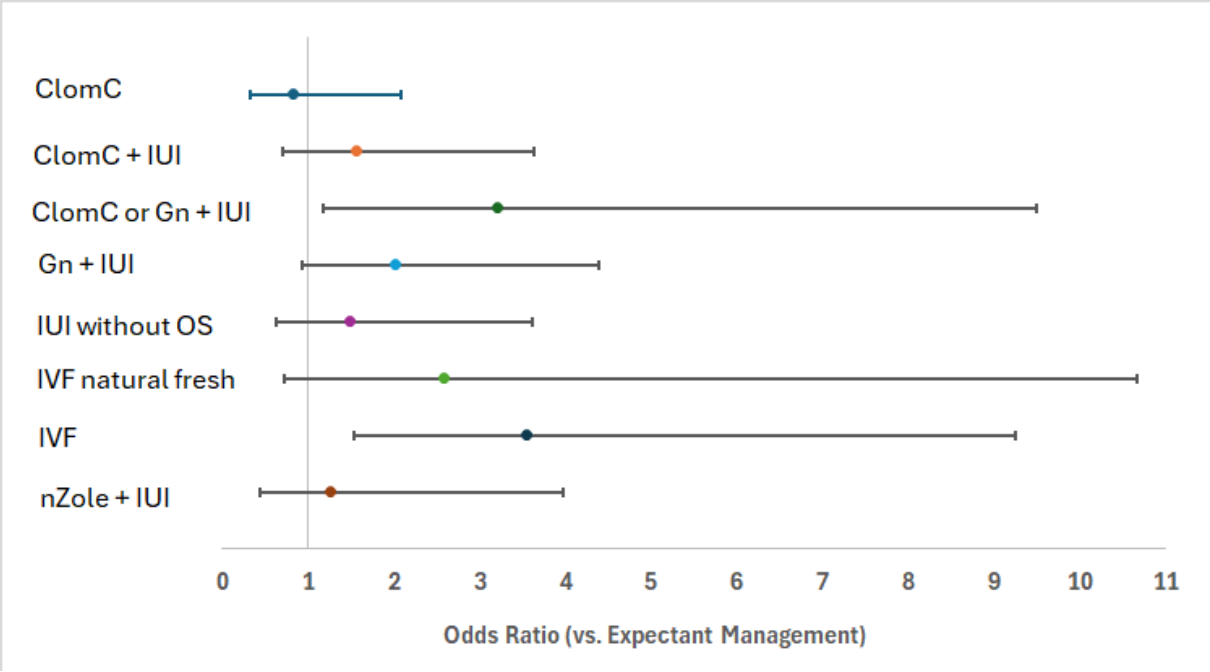
The network plot for this outcome is shown in Figure 1. Odds ratio for interventions relative to expectant management are illustrated in Figure 2 (forest plot) and odds ratios and log odds ratios relative to expectant management are compared in Table 4. Median treatment ranks and probability of being the best treatment are given in Table 5.

Figure 1. Live birth network plot – full dataset containing 16 RCTs, 37 treatment arms, 9 interventions, 4755 participants



IUI: intrauterine insemination; in vitro fertilisation; OS: ovarian stimulation

Figure 2. Live birth forest plot – full dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and expectant management. Values on the right of the vertical reference line indicate better effect compared with expectant management



Results from a random effects NMA with between study SD 0.51 (95% CrI 0.19 to 1.01)
ClomC: clomiphene citrate; CrI: credible intervals; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; nZole: anastrozole or letrozole; OS: ovarian stimulation; SD: standard deviation

Table 4: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, live birth full dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate	0.82 (0.32,2.09)	-0.20 (-1.14,0.74)
Clomiphene citrate + IUI	1.56 (0.70,3.63)	0.44 (-0.35,1.29)
Gonadotropin or clomiphene citrate + IUI	3.20 (1.17,9.49)	1.16 (0.16,2.25)
Gonadotropin + IUI	2.02 (0.93,4.39)	0.70 (-0.07,1.48)
IUI without OS	1.49 (0.62,3.62)	0.40 (-0.47, 1.29)
IVF natural fresh	2.59 (0.71,10.67)	0.95 (-0.34,2.37)
IVF	3.54 (1.52,9.25)	1.26 (0.42,2.23)
Anastrozole/Letrozole + IUI	1.26 (0,43,3.96)	0.23 (-0.84,1.38)

Results from a random effects NMA with between study SD 0.51 (95% CrI 0.19 to 1.01)
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio; SD: standard deviation

Table 5: Median treatment ranks and probability of being the best treatment for all interventions for live birth full dataset

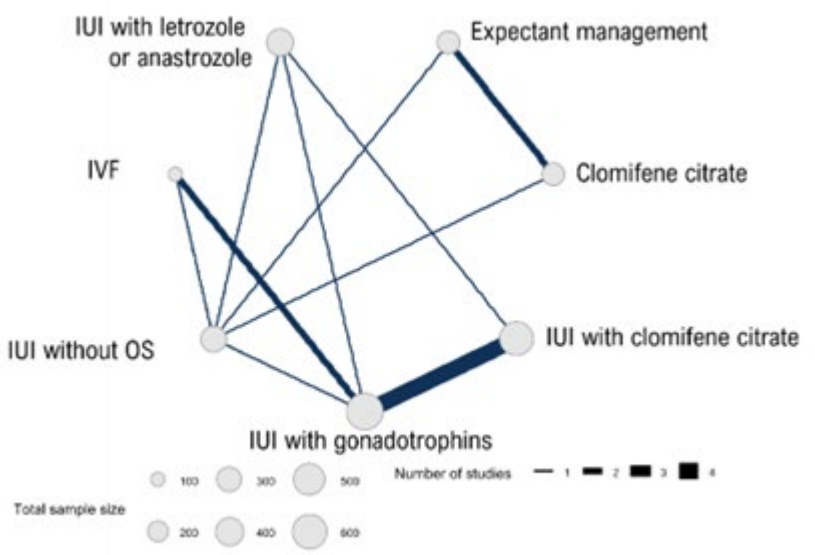
Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	8 (5,9)	0%
Clomiphene citrate	9 (4,9)	0%
Clomiphene citrate + IUI	6 (3,8)	0%
Gonadotropin or clomiphene citrate + IUI	2 (1,7)	32%
Gonadotropin + IUI	4 (2,7)	1%
IUI without OS	6 (2,9)	1%
IVF natural fresh	3 (1,8)	19%
IVF	2 (1,4)	46%
Anastrozole/Letrozole + IUI	7 (2,9)	1%

CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Mixed prognosis

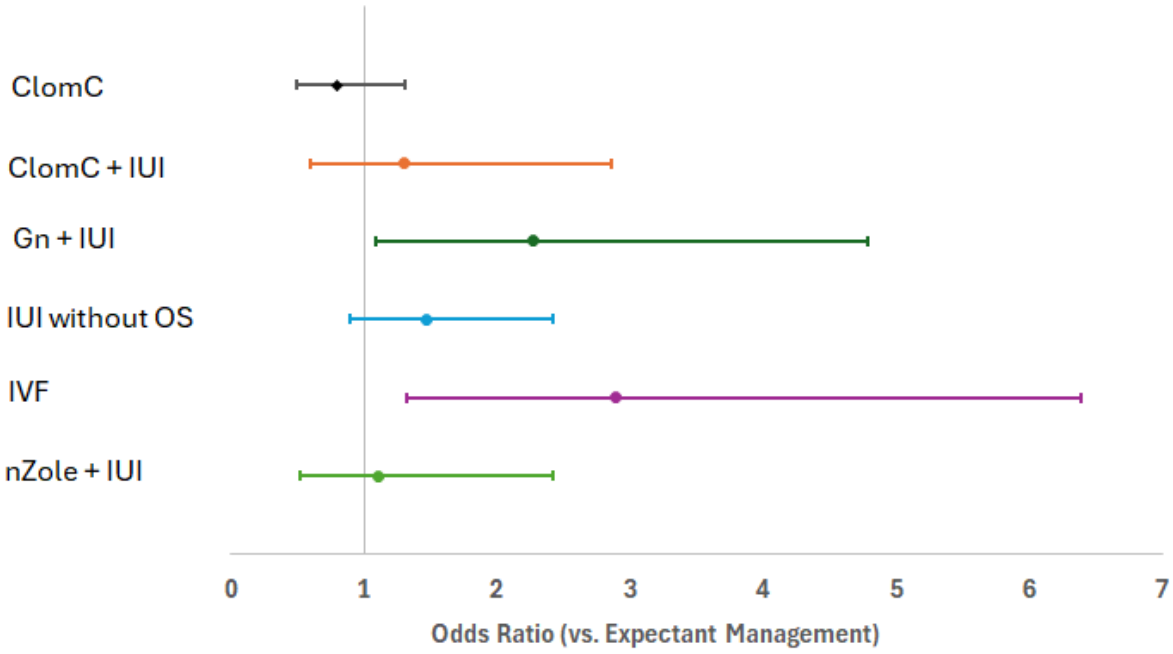
The mixed prognosis analysis was undertaken for studies where enrolment in the study was not restricted to those with a poor prognosis. The network plot for this outcome is shown in Figure 3. Odds ratio for interventions relative to expectant management are illustrated in Figure 4 (forest plot) and odds ratios and log odds ratios relative to expectant management are compared in Table 6. Median treatment ranks and probability of being the best treatment are given in Table 7.

Figure 3. Live birth network plot – mixed prognosis dataset containing 9 RCTs, 21 treatment arms, 7 interventions, 2533 participants



IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Figure 4. Live birth forest plot – mixed prognosis dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and expectant management. Values on the right of the vertical reference line indicate better effect compared with expectant management



Results from a fixed effects NMA
ClomC: clomiphene citrate; CrI: credible intervals; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; nZole: anastrozole or letrozole; OS: ovarian stimulation

Table 6: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, live birth mixed prognosis dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate	0.80 (0.49,1.31)	-0.22 (-0.71,0.28)

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate + IUI	1.30 (0.60,2.86)	0.27 (-0.50,1.05)
Gonadotropin + IUI	2.27 (1.09,4.79)	0.82 (0.08,1.57)
IUI without OS	1.47 (0.90,2.42)	0.39 (-0.11,0.88)
IVF	2.89 (6.38,1.32)	1.06 (0.28,1.85)
Anastrozole/Letrozole + IUI	1.12 (0.52,2.42)	0.11 (-0.66,0.88)

Results from a fixed effects NMA
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio; SD: standard deviation

Table 7: Median treatment ranks and probability of being the best treatment for all interventions for live birth mixed prognosis dataset

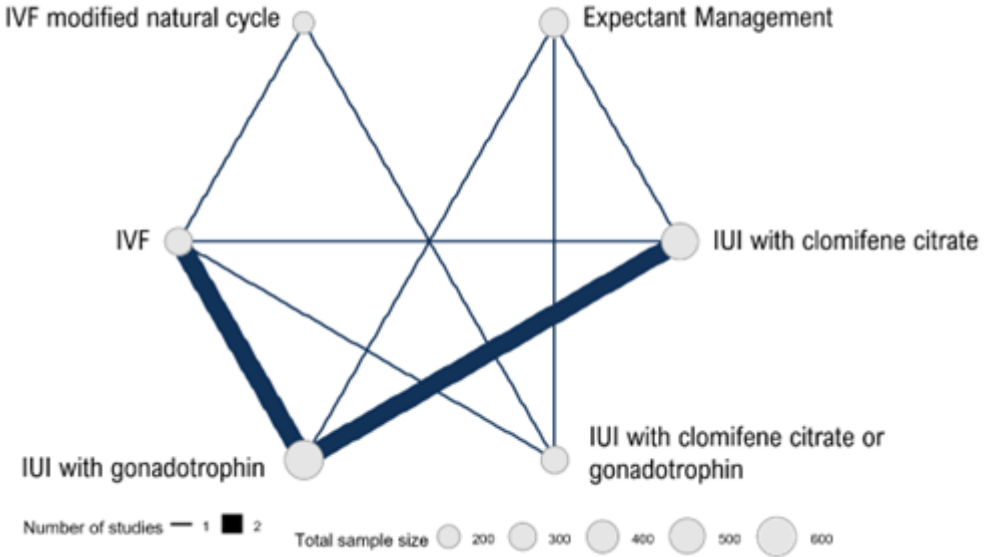
Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	6 (3,7)	0%
Clomiphene citrate	7 (4,7)	0%
Clomiphene citrate + IUI	4 (3,7)	0%
Gonadotropin + IUI	2 (1,3)	20%
IUI without OS	3 (2,5)	0%
IVF	1 (1,2)	80%
Anastrozole/Letrozole + IUI	5 (3,7)	0%

CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Poor prognosis

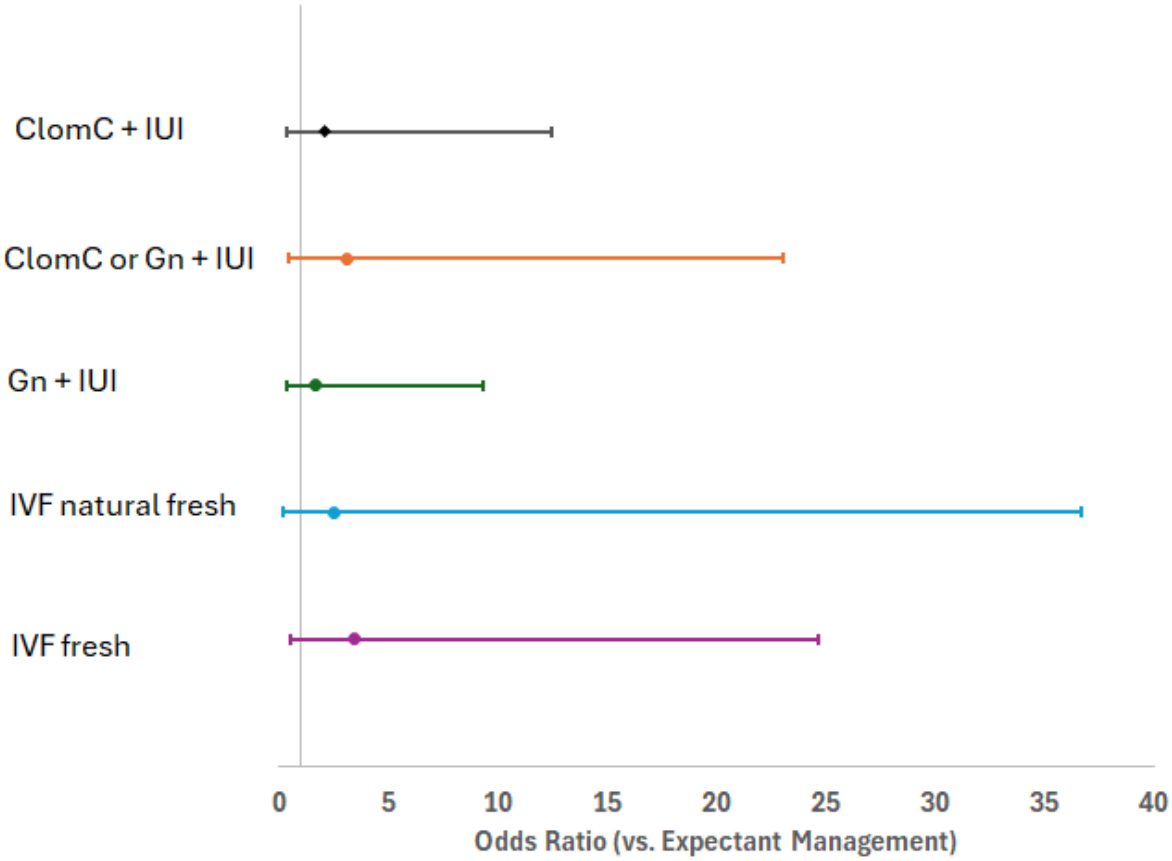
The poor prognosis analysis was undertaken for studies where the study population was estimated to have less than a 30% chance of a live birth from natural conception in the next year using the Hunault prediction model. The network plot for this outcome is shown in Figure 5. Odds ratio for interventions relative to expectant management are illustrated in Figure 6 (forest plot) and odds ratios and log odds ratios are compared in Table 8. Median treatment ranks and probability of being the best treatment are given in

Figure 5: Live birth network plot – poor prognosis dataset containing 6 RCTs, 16 treatment arms, 6 interventions, 2242 participants



IUI: intrauterine insemination; IVF: in vitro fertilisation

Figure 6: Live birth forest plot – poor prognosis dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and expectant management. Values on the right of the vertical reference line indicate better effect compared with expectant management



Results from a random effects NMA with between study SD 0.78 (95% CrI 0.24 to 2.68)
ClomC: clomiphene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; SD: standard deviation

Table 8: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, live birth poor prognosis dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate + IUI	2.08 (0.39,12.5)	0.73 (-0.94,2.53)
Gonadotropin or clomiphene citrate + IUI	3.16 (0.48,23.08)	1.15 (-0.73,3.14)
Gonadotropin + IUI	1.71 (0.33,9.35)	0.54 (-1.11,2.24)
IVF natural fresh	2.54 (0.20,36.63)	0.93 (-1.63,3.60)
IVF	3.44 (0.53,24.66)	1.23 (-0.64,3.21)

Results from a random effects NMA with between study SD 0.78 (95% CrI 0.24 to 2.68)
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio; SD: standard deviation

Table 9: Median treatment ranks and probability of being the best treatment for all interventions for live birth poor prognosis dataset

Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	6 (2,6)	1%
Clomiphene citrate + IUI	4 (1,6)	11%
Gonadotropin or clomiphene citrate + IUI	2 (1,6)	29%
Gonadotropin + IUI	4 (1,6)	3%
IVF natural fresh	3 (1,6)	21%
IVF	2 (1,5)	35%

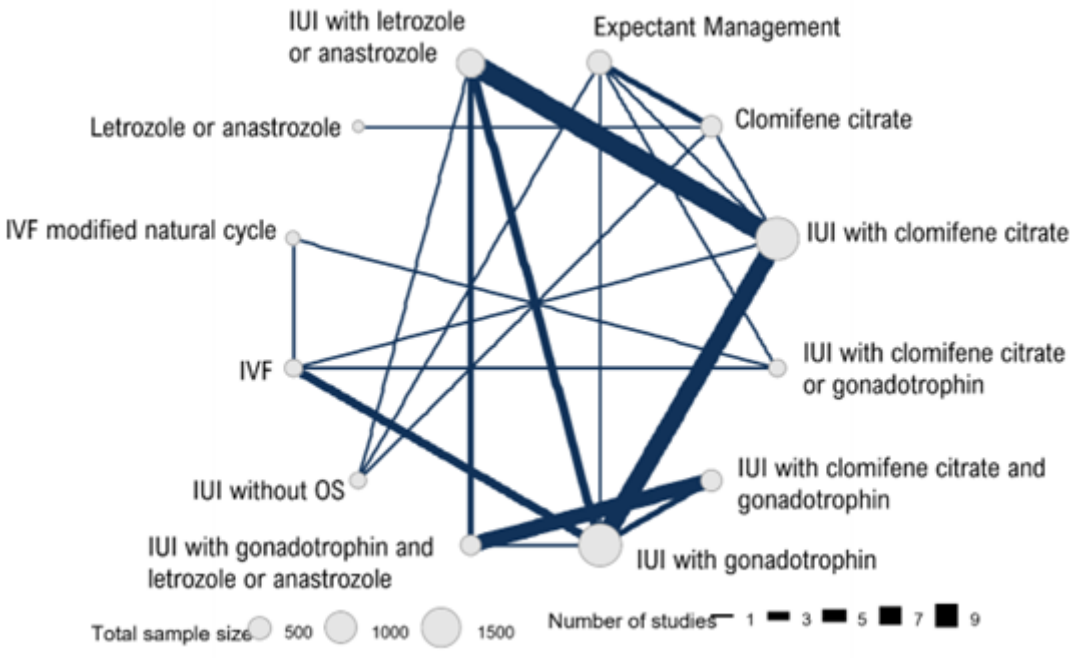
CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation

Clinical pregnancy

Full dataset

The network plot for this outcome is shown in Figure 7. Odds ratio for interventions relative to expectant management are illustrated in Figure 8 (forest plot) and odds ratios and log odds ratios relative to expectant management are compared in Table 10. Median treatment ranks and probability of being the best treatment are given in Table 11.

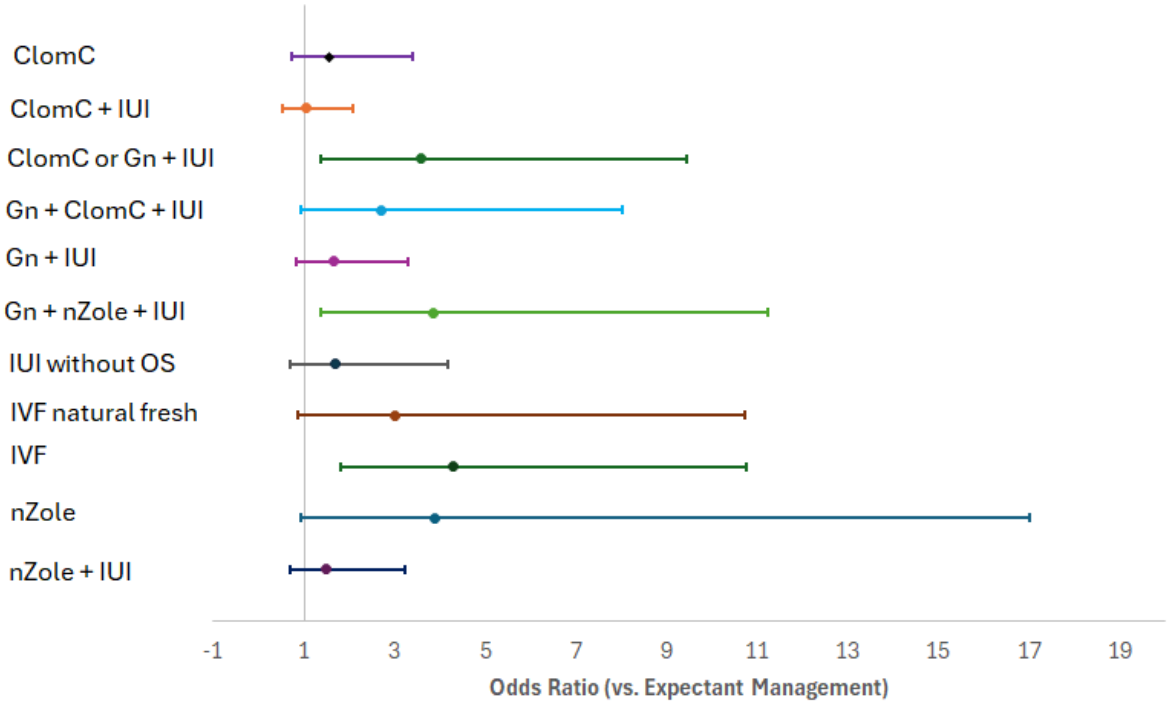
Figure 7. Clinical pregnancy network plot – full dataset containing 36 RCTs, 77 treatment arms, 12 interventions, 7406 participants



IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Figure 8. Clinical pregnancy forest plot – full dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and expectant

management. Values on the right of the vertical reference line indicate better effect compared with expectant management



Results from a random effects NMA with between study SD 0.50 (95% CrI 0.30 to 0.78)
ClomC: clomiphene citrate; CrI: credible intervals; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; nZole: anastrozole or letrozole; OS: ovarian stimulation; SD: standard deviation

Table 10: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, clinical pregnancy full dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate	1.57 (0.74, 3.39)	0.45 (-0.31, 1.22)
Clomiphene citrate + IUI	1.06 (0.53, 2.09)	0.05 (-0.63, 0.74)
Gonadotropin or clomiphene citrate + IUI	3.57 (1.37, 9.44)	1.27 (0.32, 2.25)
Gonadotropin + clomiphene citrate + IUI	2.72 (0.94, 8.02)	1.00 (-0.07, 2.08)
Gonadotropin + IUI	1.65 (0.83, 3.28)	0.50 (-0.19, 1.19)
Gonadotropin + Anastrozole/Letrozole + IUI	3.86 (1.35, 11.23)	1.35 (0.30, 2.42)
IUI without OS	1.68 (0.69, 4.18)	0.52 (-0.38, 1.43)
IVF natural fresh	3.01 (0.87, 10.73)	1.10 (-0.15, 2.37)
IVF	4.30 (1.79, 10.75)	1.46 (0.58, 2.38)
Anastrozole/Letrozole	3.88 (0.92, 17.01)	1.36 (-0.08, 2.83)
Anastrozole/Letrozole + IUI	1.48 (0.70, 3.23)	0.39 (-0.36, 1.17)

Results from a random effects NMA with between study SD 0.50 (95% CrI 0.30 to 0.78)
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio; SD: standard deviation

Table 11: Median treatment ranks and probability of being the best treatment for all interventions for clinical pregnancy full dataset

Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	11 (8, 12)	0%
Clomiphene citrate	8 (4, 8)	0%
Clomiphene citrate + IUI	11 (8, 12)	0%

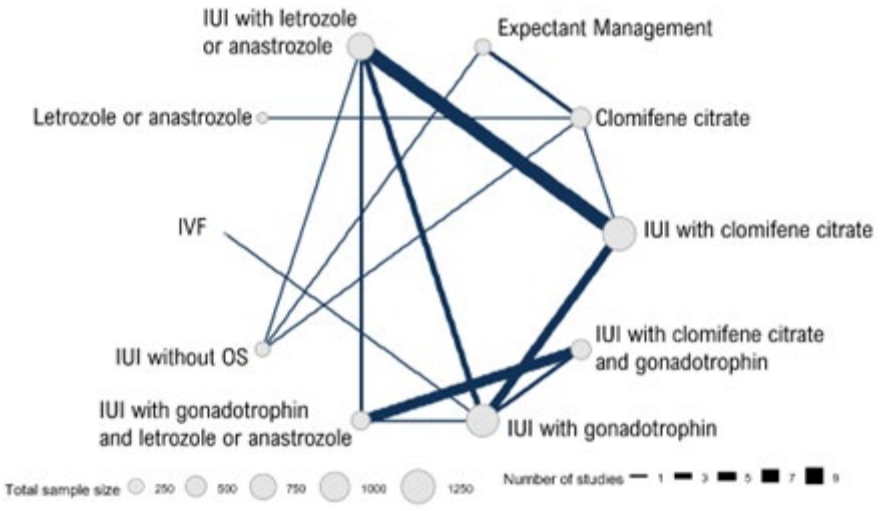
Intervention	Median (95% CrI) treatment rank	Probability of being best
Gonadotropin or clomiphene citrate + IUI	4 (1, 9)	12%
Gonadotropin + clomiphene citrate + IUI	5 (2, 10)	2%
Gonadotropin + IUI	8 (5, 11)	0%
Gonadotropin + Anastrozole/Letrozole + IUI	3 (1, 7)	21%
IUI without OS	8 (3, 12)	0%
IVF natural fresh	5 (1, 11)	10%
IVF	2 (1, 6)	23%
Anastrozole/Letrozole	3 (1, 11)	32%
Anastrozole/Letrozole + IUI	9 (5, 12)	0%

CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Mixed prognosis

The mixed prognosis analysis was undertaken for studies where enrolment in the study was not restricted to those with a poor prognosis. The network plot for this outcome is shown in Figure 9. Odds ratio for interventions relative to expectant management are illustrated in Figure 10 (forest plot) and odds ratios and log odds ratios relative to expectant management are compared in Table 12. Median treatment ranks and probability of being the best treatment are given in Table 13.

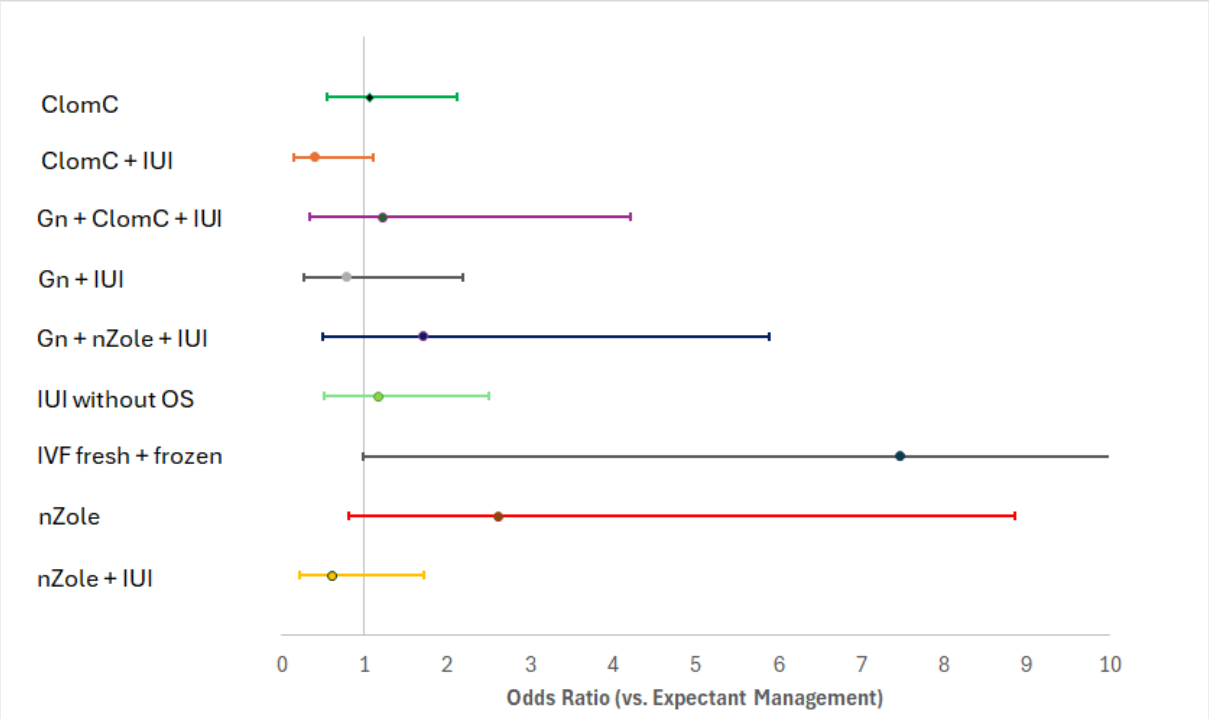
Figure 9. Clinical pregnancy network plot – mixed prognosis dataset containing 29 RCTs, 61 treatment arms, 10 interventions, 5164 participants



IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Figure 10. Clinical pregnancy forest plot – mixed prognosis dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and

expectant management. Values on the right of the vertical reference line indicate better effect compared with expectant management



Results from a random effects NMA with between study SD 0.32 (95% CrI 0.07 to 0.61)
ClomC: clomiphene citrate; CrI: credible intervals; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; nZole: anastrozole or letrozole; OS: ovarian stimulation; SD: standard deviation

Table 12: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, clinical pregnancy mixed prognosis dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate	1.06 (0.55,2.12)	0.06 (-0.61,0.75)
Clomiphene citrate + IUI	0.40 (0.14,1.10)	-0.91 (-1.95,0.10)
Gonadotropin + clomiphene citrate + IUI	1.22 (0.35,4.22)	0.20 (-1.06,1.44)
Gonadotropin + IUI	0.78 (0.26,2.19)	-0.25 (-1.34,0.78)
Gonadotropin + Anastrozole/Letrozole + IUI	1.71 (0.49,5.89)	0.54 (-0.71,1.77)
IUI without OS	1.16 (0.51,2.49)	0.15 (-0.67,0.91)
IVF	7.47 (0.99,65.22)	2.01 (-0.01,4.18)
Anastrozole/Letrozole	2.62 (0.81,8.86)	0.96 (-0.21,2.18)
Anastrozole/Letrozole + IUI	0.60 (0.22,1.71)	-0.51 (-1.53,0.54)

Results from a random effects NMA with between study SD 0.32 (95% CrI 0.07 to 0.61)
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio; SD: standard deviation

Table 13: Median treatment ranks and probability of being the best treatment for all interventions for clinical pregnancy mixed prognosis dataset

Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	6 (3,10)	4%
Clomiphene citrate	6 (3,9)	2%
Clomiphene citrate + IUI	10 (9,10)	0%
Gonadotropin + clomiphene citrate + IUI	5 (2,8)	4%
Gonadotropin + IUI	8 (4,9)	0%

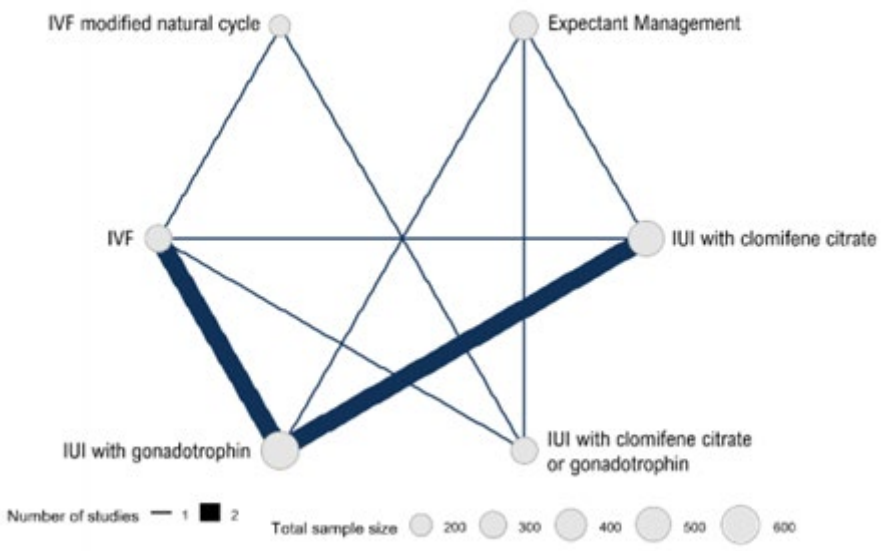
Intervention	Median (95% CrI) treatment rank	Probability of being best
Gonadotropin + Anastrozole/Letrozole + IUI	3 (2,7)	15%
IUI without OS	5 (2,9)	5%
IVF	1 (1,5)	39%
Anastrozole/Letrozole	2 (1,6)	37%
Anastrozole/Letrozole + IUI	9 (6,9)	0%

CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Poor prognosis

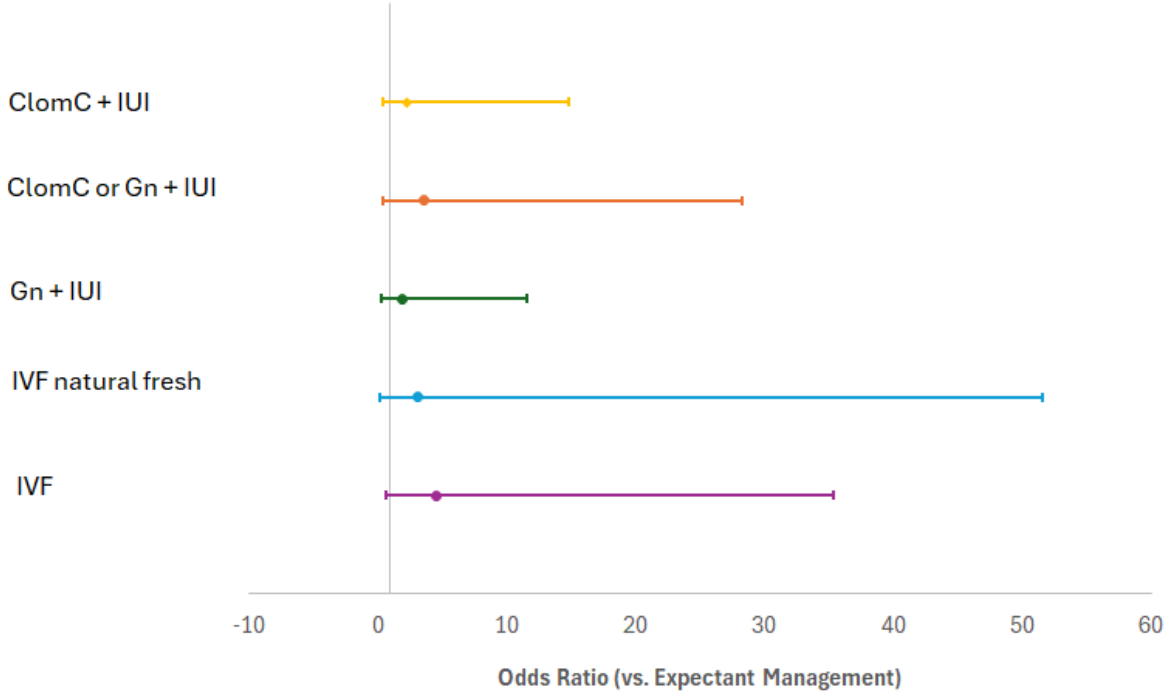
The poor prognosis analysis was undertaken for studies where the study population was estimated to have less than a 30% chance of a live birth from natural conception in the next year using the Hunault prediction model. The network plot for this outcome is shown in Figure 11. Odds ratio for interventions relative to expectant management are illustrated in Figure 12 (forest plot) and odds ratios and log odds ratios are compared in Table 14. Median treatment ranks and probability of being the best treatment are given in Table 15.

Figure 11: Clinical pregnancy network plot – poor prognosis dataset containing 7 RCTs, 16 treatment arms, 6 interventions, 2242 participants



IUI: intrauterine insemination; IVF: in vitro fertilisation

Figure 12: Clinical pregnancy forest plot – poor prognosis dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and expectant management. Values on the right of the vertical reference line indicate better effect compared with expectant management



Results from a random effects NMA with between study SD 0.83 (95% CrI 0.26 to 2.83)
Abbreviations: ClomC: clomiphene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; SD: standard deviation

Table 14: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, clinical pregnancy poor prognosis dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate + IUI	2.24 (0.38, 14.80)	0.81 (-0.98, 2.69)
Gonadotropin or clomiphene citrate + IUI	3.65 (0.47, 28.26)	1.30 (-0.75, 3.34)
Gonadotropin + IUI	1.91 (0.33, 11.53)	0.65 (-1.10, 2.45)
IVF natural fresh	3.13 (0.20, 51.62)	1.14 (-1.62, 3.94)
IVF	4.52 (0.62, 35.41)	1.51 (-0.48, 3.57)

Results from a random effects NMA with between study SD 0.83 (95% CrI 0.26 to 2.83)
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio; SD: standard deviation

Abbreviations

Table 15: Median treatment ranks and probability of being the best treatment for all interventions for clinical pregnancy poor prognosis dataset

Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	6 (2, 6)	1%
Clomiphene citrate + IUI	4 (1,6)	8%
Gonadotropin or clomiphene citrate + IUI	2 (1, 6)	25%
Gonadotropin + IUI	4 (1, 6)	3%
IVF natural fresh	3 (1, 6)	21%

Intervention	Median (95% CrI) treatment rank	Probability of being best
IVF	2 (1, 5)	42%

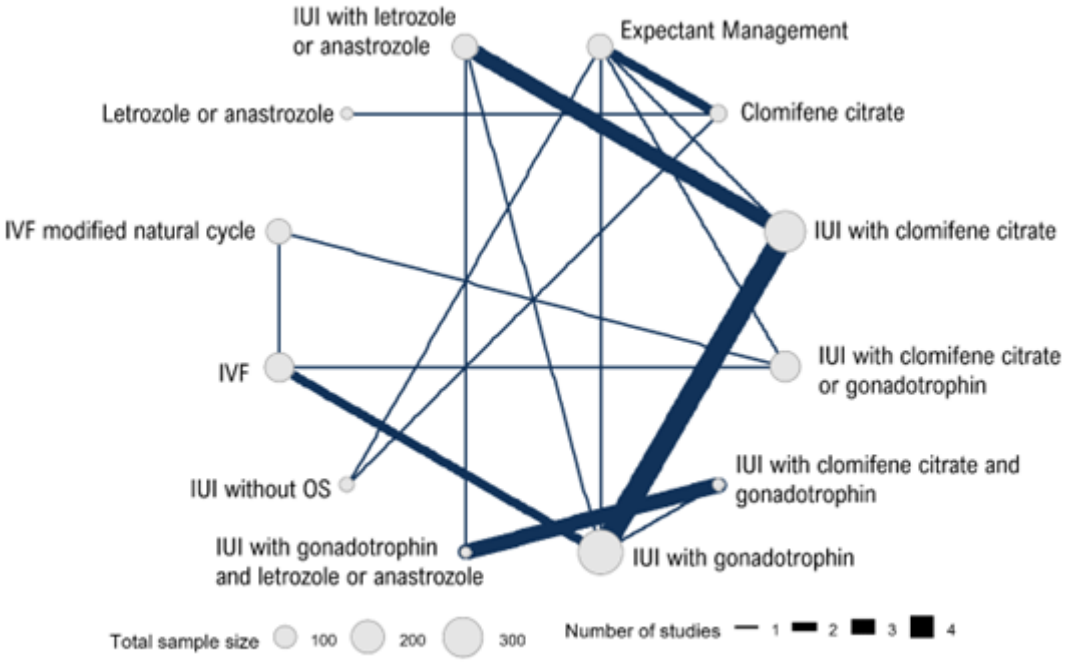
CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation

Multiple pregnancy

Full dataset

The network plot for this outcome is shown in Figure 13. Odds ratio for interventions relative to expectant management are illustrated in Figure 14 (forest plot) and odds ratios and log odds ratios relative to expectant management are compared in Table 16. Median treatment ranks and probability of being the best treatment are given in Table 17.

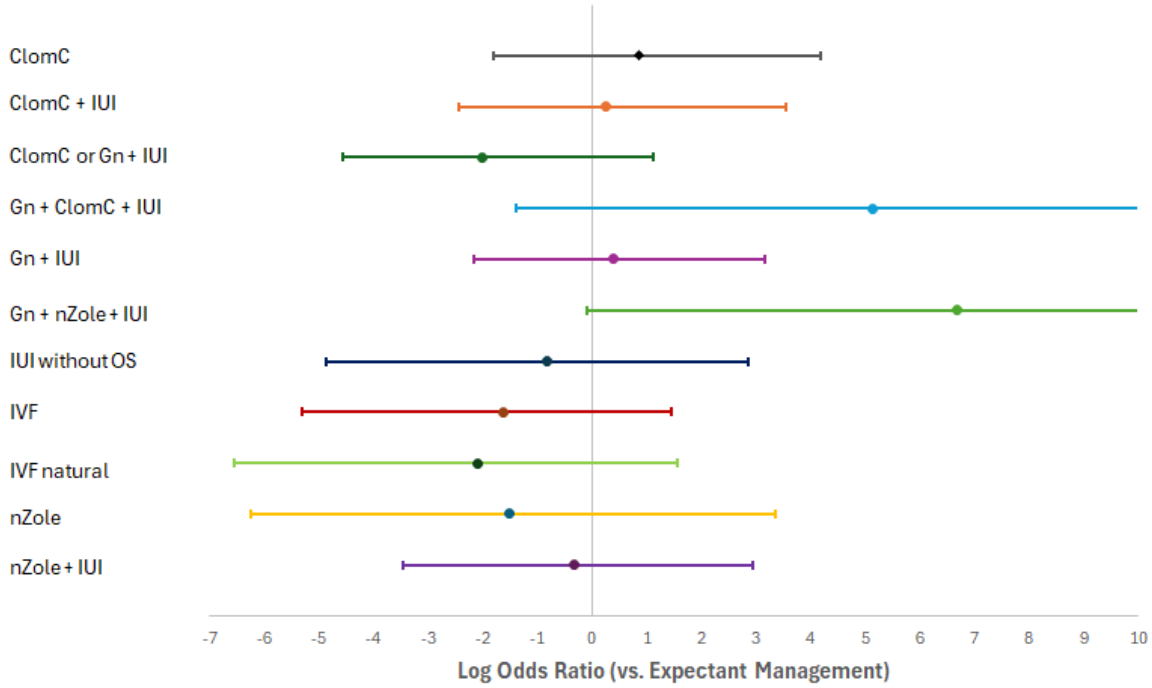
Figure 13. Multiple pregnancy network plot – full dataset containing 20 RCTs, 43 treatment arms, 12 interventions, 1553 pregnancies



IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Figure 14. Multiple pregnancy forest plot – full dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and expectant

management. Values on the right of the vertical reference line indicate better effect compared with expectant management (note: scale is log odds ratios)



Results from a random effects NMA with between study SD 1.03 (95% CrI 0.27 to 2.88)
ClomC: clomiphene citrate; CrI: credible intervals; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; nZole: anastrozole or letrozole; OS: ovarian stimulation; SD: standard deviation

Table 16: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, multiple pregnancy full dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate	2.37 (0.16,64.87)	0.86 (-1.81,4.117)
Clomiphene citrate + IUI	1.29 (0.10,29.14)	0.25 (-2.31,3.372)
Gonadotropin or clomiphene citrate + IUI	0.13 (0.00,2.77)	-2.01 (-6.27,1.02)
Gonadotropin + clomiphene citrate + IUI	171.60 (0.25,6093000)	5.15 (-1.40,15.62)
Gonadotropin + IUI	1.48 (0.12,23.85)	0.39 (-2.16,3.17)
Gonadotropin + Anastrozole/Letrozole + IUI	795.40 (0.91,32220000)	6.68 (-0.09,17.29)
IUI without OS	0.44 (0.01,17.61)	-0.82 (-4.85,2.87)
IVF	0.20 (0.00,4.24)	-1.64 (-5.30,1.45)
IVF natural fresh	0.12 (0.00,4.77)	-2.10 (-6.54,1.56)
Anastrozole/Letrozole	0.22 (0.00,28.41)	-1.50 (-6.24,3.35)
Anastrozole/Letrozole + IUI	0.72 (0.03,19.00)	-0.33 (-3.46,2.95)

Results from a random effects NMA with between study SD 1.03 (95% CrI 0.27 to 2.88)
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio; SD: standard deviation

Table 17: Median treatment ranks and probability of being the best treatment for all interventions for multiple pregnancy full dataset

Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	7 (3,10)	0%
Clomiphene citrate	9 (3,12)	0%
Clomiphene citrate + IUI	8 (3,10)	0%

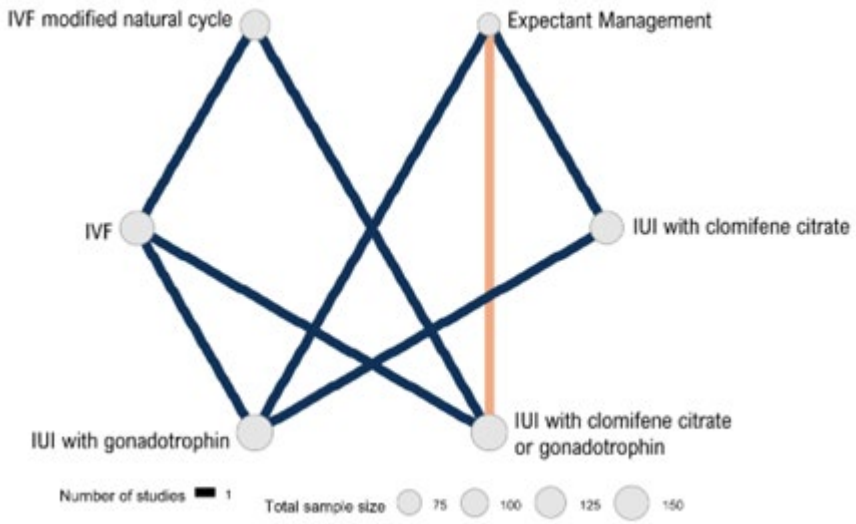
Intervention	Median (95% CrI) treatment rank	Probability of being best
Gonadotropin or clomiphene citrate + IUI	3 (1,8)	20%
Gonadotropin + clomiphene citrate + IUI	11 (5,12)	0%
Gonadotropin + IUI	8 (4,10)	0%
Gonadotropin + Anastrozole/Letrozole + IUI	12 (8,12)	0%
IUI without OS	5 (1,11)	13%
IVF	3 (1,8)	9%
IVF natural fresh	2 (1,9)	26%
Anastrozole/Letrozole	4 (1,10)	28%
Anastrozole/Letrozole + IUI	6 (1,10)	3%

CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Poor prognosis

The poor prognosis analysis was undertaken for studies where the study population was estimated to have less than a 30% chance of a live birth from natural conception in the next year using the Hunault prediction model. The network plot for this outcome is shown in Figure 15. Odds ratio for interventions relative to expectant management are illustrated in Figure 16 (forest plot) and odds ratios and log odds ratios relative to expectant management are compared in Table 18. Median treatment ranks and probability of being the best treatment are given in Table 19.

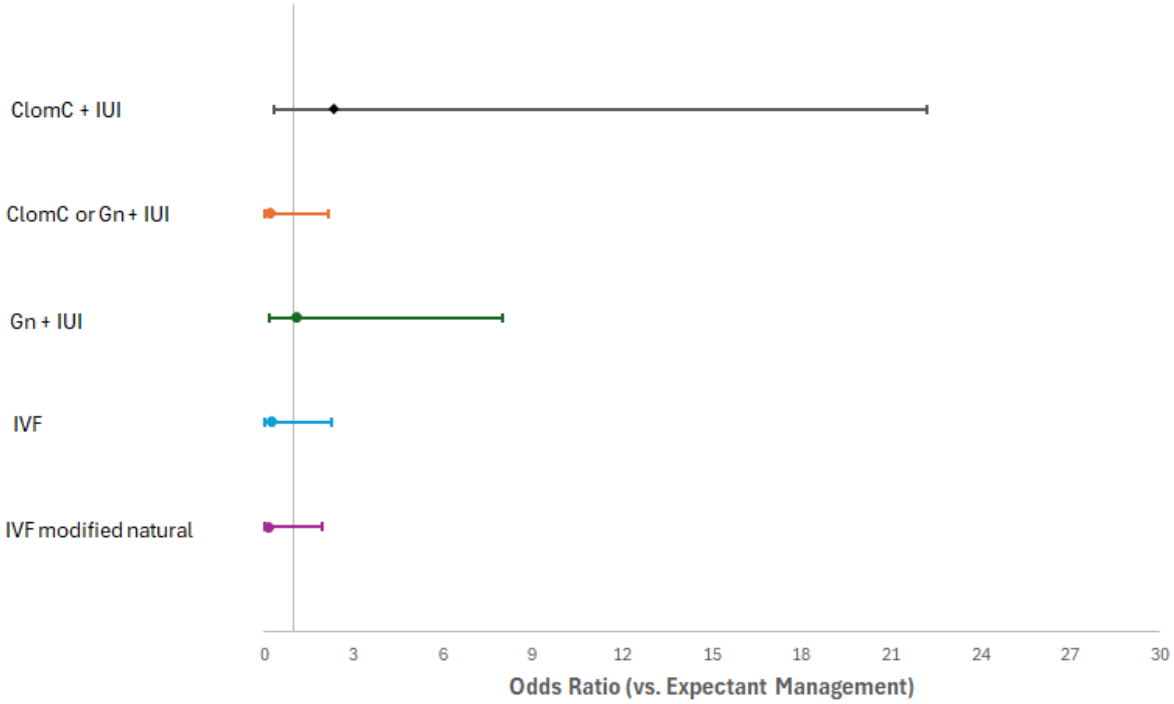
Figure 15. Multiple network plot – poor prognosis dataset containing 6 RCTs, 13 treatment arms, 6 interventions, 1249 pregnancies



IUI: intrauterine insemination; IVF: in vitro fertilisation

Figure 16. Multiple pregnancy forest plot – poor prognosis dataset. Vertical reference line at 1 indicates no difference in odds of the outcome between the intervention and

expectant management. Values on the right of the vertical reference line indicate better effect compared with expectant management



Results from a fixed effects NMA
Vertical axis shows effect of no treatment. Values on the right of the vertical axis indicate better effect compared with expectant management
ClomC: clomiphene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMA: network meta-analysis; OS: ovarian stimulation

Table 18: Odds ratio, log odds ratio and 95% CrIs for all interventions compared with expectant management, multiple pregnancy poor prognosis dataset

Intervention	NMA OR (95% CrI)	NMA LOR (95% CrI)
Clomiphene citrate + IUI	2.34 (0.31,22.21)	0.85 (-1.16,3.10)
Gonadotropin or clomiphene citrate + IUI	0.23 (0.02,2.14)	-1.48 (-3.97,0.76)
Gonadotropin + IUI	1.08 (0.16,7.97)	0.08 (-1.81,2.08)
IVF	0.24 (0.02,2.25)	-1.44 (-3.90,0.81)
IVF natural	0.17 (0.01,1.92)	-1.75 (-4.39,0.66)

Results from a fixed effects NMA
CrI: Credible intervals; LOR: log odds ratio; NMA: network meta-analysis; OR: odds ratio

Table 19: Median treatment ranks and probability of being the best treatment for all interventions for multiple pregnancy poor prognosis dataset

Intervention	Median (95% CrI) treatment rank	Probability of being best
Expectant management	4 (1,6)	4%
Clomiphene citrate + IUI	6 (4,6)	0%
Gonadotropin or clomiphene citrate + IUI	2 (1,5)	23%
Gonadotropin + IUI	5 (2,6)	2%
IVF	2 (1,4)	19%
IVF natural	1 (1,4)	53%

CrI: Credible intervals; IUI: intrauterine insemination; IVF: in vitro fertilisation

Quality assessment of the NMA

Threshold analysis was undertaken to test the robustness of treatment recommendations based on the NMA of live birth to potential biases or sampling variation in the included evidence.

When considering the entire population and the sub-population with a mixed prognosis (excluding studies restricted to those with a poor prognosis), the finding that IVF was the most effective treatment was consistent.

Threshold analysis identified instances where minor variations in individual study results could shift the preferred treatment from IVF to IUI with gonadotrophins (in the fixed-effect NMA model for populations with mixed prognosis) or from IVF to IUI with clomifene citrate or gonadotrophins (in the random-effect NMA model for populations with any prognosis).

Full methods and results of the threshold analysis are presented in appendix M.

Summary of the evidence from the pairwise comparisons

Important outcomes in a mixed prognosis population

Very low to low quality evidence showed no important differences for pregnancy loss (as a proportion of the number of clinical pregnancies) in a mixed prognosis population for the following comparisons: clomifene citrate relative to expectant management, or relative to IUI (without ovarian stimulation); IUI (without ovarian stimulation) relative to expectant management; IUI with clomifene citrate relative to IUI with letrozole/anastrozole; IUI with letrozole/anastrozole relative to IUI (without ovarian stimulation), or relative to IUI with gonadotropin; IUI with gonadotropin and clomifene citrate relative to IUI with gonadotropin and letrozole/anastrozole; or IVF relative to IUI with gonadotropin.

There was low quality evidence for a higher rate of pregnancy loss (as a proportion of clinical pregnancies) for those receiving IUI with clomifene citrate relative to those receiving IUI with gonadotropin in a mixed prognosis population. Conversely there was low quality evidence for a higher rate of ovarian hyperstimulation syndrome (OHSS) in those randomised to IUI with gonadotropin relative to those randomised to IUI with clomifene citrate, although the effect could only be estimated in 2 of the 5 studies included for this comparison due to zero events in both arms for the other 3 studies.

There was very limited evidence for the outcome of OHSS as very few studies reported this outcome and those that did included a lot of zero events. Effects could not be estimated for the clomifene citrate relative to letrozole/anastrozole comparison, IUI with clomifene citrate relative to IUI with letrozole/anastrozole, or IVF relative to IUI with gonadotropin, in a mixed prognosis population due to zero events in both arms. Low quality evidence showed no important difference in OHSS between those receiving IUI with letrozole/anastrozole and those receiving IUI with gonadotropin. Very low quality evidence also showed no important difference in OHSS between those receiving IUI with gonadotropin and clomifene citrate relative to those receiving IUI with gonadotropin and letrozole/anastrozole.

Important outcomes in a poor prognosis population

Very low to low quality evidence showed no important differences for pregnancy loss (as a proportion of the number of clinical pregnancies) in a poor prognosis population for the following comparisons: IUI with clomifene citrate relative to expectant management, or relative to IUI with gonadotropin; IUI with gonadotropin relative to expectant management; IVF relative to IUI with clomifene citrate, or relative to IUI with gonadotropin, or relative to IUI with either clomifene citrate or a gonadotropin used as ovarian stimulation agents; IVF (conventional) relative to IVF modified natural cycle; or IVF modified natural cycle relative to IUI with clomifene citrate/gonadotropin.

Very low quality evidence showed no important differences for OHSS in a poor prognosis population for the following comparisons: IVF relative to IUI with either clomifene citrate or a gonadotropin used as ovarian stimulation agents; IVF relative to IVF modified natural cycle; or IVF modified natural cycle relative to IUI with clomifene citrate/gonadotropin. Although all evidence for this outcome came from a single RCT.

See appendix F for full GRADE tables.

Economic evidence

A total of 6,427 studies were identified in the health economic literature search for this review question. After duplicates were removed, 4,314 studies were sifted on title and abstract. Of these studies, 39 were ordered, and sifted, for full text review. 11 of the 39 studies were formally checklisted for inclusion – and of these studies, five were excluded and six were included in the evidence review.

Included studies

Six economic studies were identified that were relevant to this question (van Eekelen 2020, Tjon-Kon-Fat 2015, Danhof 2020, Wordsworth 2011, van Eekelen 2021, Brordewijk 2019).

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

Excluded studies

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

Summary of included economic evidence

See Table 20 for the economic evidence profile of the included studies.

Table 20: Economic evidence profile of a systematic review of economic evaluations for unexplained subfertility

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
van Eekelen 2020 **1.**IVF-EM-EM (immediate IVF) **2.**EM-IVF-EM (delayed IVF) **3.**EM-EM-IVF (postponed IVF) **4.**IUIOS-IVF-EM (immediate IUI) **5.**EM-IUIOS-IVF (delayed IUI)	Potentially serious limitations[1]	Partially applicable[2,3]	Decision analytic model using data from an NMA (Wang 2019) **Time Horizon:** 3-years with each intervention for the comparators representing 1-year **Country:** Netherlands **Cost year:** 2018 **Perspective:** Societal (healthcare perspective reported in a sensitivity analysis – healthcare perspective reported in this Table)	Compared to the reference case EM-EM-IVF **(3)** **1.** €1,194 **2.** €362 **3.** €0 **4.** €1,674 **5.** €800	Compared to the reference case EM-EM-IVF **(3)** **1.** -2.1% **2.** -0.5% **3.** 0 **4.** 5.8% **5.** 8.4% *Expressed as cumulative probability of live birth*	Intervention **1** dominated by intervention **3** Intervention **2** dominated by intervention **3** Intervention **3 – *reference case (0)*** Intervention **4** dominated by intervention **5** ICER for intervention **5**: €9,443 per live birth (when analysed from a health care perspective) *€31,141 (when analysed from a societal perspective)*	EM-EM-IVF (intervention 3) has the probability of having the highest NMB – i.e. being the most cost-effective

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Tjon-Kon-Fat 2015 IVF single embryo transfer (SET) IVF with mildly stimulated or modified natural cycle (MNC) Compared with IUI with controlled ovarian hyperstimulation (COH)	Potentially serious limitations[4]	Partially applicable[5]	Within-trial analysis **Country**: Netherlands **Time Horizon:** 1 year **Cost year:** 2013 **Perspective:** Healthcare	Difference between IVF-SET and IUI-COH was €2,117 and between IVF-MNC and IUI-COH €3,136	IVF-SET versus IUI-COH RR – 1.1 IVF-MNC versus IUI-COH RR – 0.91 Live birth a health child: IVF-SET: 104/201 IVF-MNC: 83/194 IUI-COH: 97/207	IVF-SET compared with IUI-COH was €43,375 reflecting the additional costs necessary to achieve one additional healthy child IVF-MNC compared with IUI-COH was negative (€76, 925) and IUI-COH was the dominant strategy *(less costly and more effective)*	For IVF-SET compared to IUI-COH: At a willingness-to-pay of €60,000 for an additional healthy child, there is a 62% chance that IVF-SET is cost-effective. At a willingness-to-pay of €135,000, there is an 81% chance that IVF-SET is cost-effective For IVF-MNC compared with IUI-COH, IUI-COH was dominant and therefore a CEAC was not plotted
Danhof 2020 Gonadotrophins compared to Clomiphene citrate	Potentially serious limitations[6]	Partially applicable[7]	Within-trial analysis **Country:** Netherlands **Time Horizon:** 6-months **Cost year**: 2017 **Perspective:** Healthcare	€468	5% -ongoing pregnancy rate Relative risk 1.16	€21,804 per additional ongoing pregnancy €17,044 per additional live birth	

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Wordsworth 2011 Clomifene citrate (CC) Intrauterine Insemination (IUI) Expectant management (EM)	Potentially serious limitations[8]	Partially applicable[9]	Post-trial economic analysis **Country**: UK **Time Horizon:** 6-months **Cost year:** 2006 **Perspective:** Healthcare	IUI versus EM: £319.39 CC versus IUI: £18.69 *Mean costs:* *EM: £11.88* *IUI: £331.27* *CC: £349.96*	IUI versus EM: 0.06 CC versus IUI: -0.09 *Live birth rate:* *EM: 0.17* *IUI: 0.22* *CC: 0.13*	CC: Dominated *(more costly and less effective compared to EM + IUI)* £5,604 cost per live birth for IUI compared to EM	At £10,000 for an additional live birth IUI is cost-effective with a probability of ~70% At £4,000 for an additional live birth IUI is cost-effective with a probability of ~30%. If the cost–effectiveness ceiling ratio is £30,000: EM has a ~15% chance of being the most cost-effective intervention, while IUI has an ~80% chance
van Eekelen 2021 Letrozole + IUI Gonadotrophins + IUI Compared to Clomifene citrate (CC) + IUI	Minor limitations[10]	Partially applicable[11]	Decision analytic model **Country:** Netherlands **Time Horizon:** Four cycles of IUI to completed within a year **Cost year:** 2019 **Perspective:** Healthcare (because cost for procedures associated with IUI treatment	Compared to CC: Letrozole €72 Gonadotrophins €1,147	Probability of live birth compared to CC (29.4%): Letrozole 2.6% Gonadotrophins 5.1%	Letrozole: €2,809 per additional cost per live birth Gonadotrophins: €53,831 per additional cost per live birth *ICERs calculated in comparison to CC*	Between €1 and €3,000 per cost per live birth, CC has the highest probability of being cost effective (maximally 65% at €1) Between €3,000 and €55,000, Letrozole had the highest probability of being cost effective (maximally 62%)

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
			were considered identical for all three agents)				Over, €55,000 or more, gonadotrophins had the highest probability of being cost effective (maximally 56%)
Brordewijk 2019 Gonadotrophins + IUI **(1)** Gonadotrophins **(2)** Clomifene citrate (CC) + IUI **(3)** Clomifene citrate (CC) **(4)** The study compared Gonadotrophins to CC • *1 + 2 compared to 3 + 4* And IUI compared to intercourse • *1 + 3 compared to 2 + 4*	Potentially serious limitations[12]	Partially applicable[13]	Within-trial analysis **Country:** Netherlands (UK costs used in a sensitivity analysis – UK costs reported in this Table_ **Time Horizon:** 8-months **Cost year**: 2017 **Perspective:** Healthcare *When UK costs were employed in the SA costs were obtained from only one UK hospital*	Gonadotrophins compared with CC: £1,918 IUI compared with intercourse: £2,093	Gonadotrophins compared with CC: Rate difference relative risk – 1.24 IUI compared with intercourse: Rate difference relative risk – 1.14	Gonadotrophins compared with CC: £19,744 cost per additional live birth IUI compared with intercourse: £34,420 cost per additional live birth	Probabilistic sensitivity analysis using bootstrapping conducted for the base case analysis where costs are obtained from Dutch specific sources and presented in euros.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
NICE guideline model 2025 IVF | EM IUI without OS | IVF | EM Clomiphene citrate + IUI | IVF | EM Gonadotropin + IUI | IVF | EM Letrozole or anastrozole + IUI | IVF | EM	Potentially serious limitations[14,15]	Directly applicable[16]	Decision analytic model using data from an NMA undertaken for this evidence review **Time Horizon:** Remaining reproductive life for live birth outcomes, and remaining life expectancy for QALYs relating to live birth **Country**: UK **Cost year:** 2022-23 Perspective: Societal (healthcare perspective reported in a sensitivity analysis – healthcare perspective reported in this Table)	**Reference treatment strategy IVF | EM** **Clomiphene citrate + IUI | IVF | EM** ruled out by extended dominance **Letrozole or anastrozole + IUI | IVF | EM** dominated by IVF | EM **IUI without OS | IVF | EM** ruled out by extended dominance **Gonadotropin + IUI | IVF | EM** £3,862	**Reference treatment strategy IVF | EM** **Clomiphene citrate + IUI | IVF | EM** ruled out by extended dominance **Letrozole or anastrozole + IUI | IVF | EM** dominated by IVF | EM **IUI without OS | IVF | EM** ruled out by extended dominance **Gonadotropin + IUI | IVF | EM** 0.095 QALYs	**Reference treatment strategy IVF | EM** **Clomiphene citrate + IUI | IVF | EM** ruled out by extended dominance **Letrozole or anastrozole + IUI | IVF | EM** dominated by IVF | EM **IUI without OS | IVF | EM** ruled out by extended dominance **Gonadotropin + IUI | IVF | EM** £40,502 per QALY	In the base case analysis IVF | EM had a 78% probability of being the most cost-effective strategy In most sensitivity analyses IVF | EM had the highest probability of being cost effective but Gonadatropin + IUI | IVF | EM became at least borderline cost-effective with higher baseline births, greater health state utility gain from a live birth and higher costs of IVF.

[1] Main analysis conducted from a societal perspective. Healthcare perspective presented as a sensitivity analysis and presented in this table. All analyses can be found in Appendix H.
[2] Dutch costs applied in the model
[3] Discount rates differ from NICE reference case (4% for costs and 1.5% for outcomes)
[4] Short time horizon that may not reflect UK practice.

[5] *Dutch costs from 2013 used in the model and therefore may be outdated and not reflect UK costs*
[6] *Short time horizon that may not reflect UK practice*
[7] *Based on a trial conducted in the Netherlands. Dutch costs employed in the model*
[8] *Short time horizon that may not reflect UK practice.*
[9] *Old UK study and therefore costs are likely outdated. The validity of IUI as comparator without IUI could be questioned and is not reflective of UK current practice.*
[10] *Analysis does not include IVF so is not reflective of the full treatment pathway in the UK.*
[11] *Dutch costs employed in the model*
[12] *Main analysis conducted using Dutch costs. Sensitivity analysis conducted using UK costs be these were obtained from only one UK hospital and therefore may not accurately reflect UK prices. CEAC not reported for UK costs. Analysis does not include IVF so is not reflective of the full treatment pathway in the UK.*
[13] *.Based on a within-trial analysis conducted in the Netherlands*
[14] *Health state utilities increment from a live birth was estimated from Health Utilities Index Mark 2 (HUI-2) rather than NICE's preferred instrument EQ-5D-3L*
[15] *Interventions in the NMA did not always have the same number of treatment cycles*
[16] *This analysis was conducted specifically to answer this review question*

Economic model

An original cost-utility analysis, utilising the results of the NMA was undertaken, to compare the following assisted reproduction strategies:

i. IVF followed by expectant management (IVF | EM)
ii. IUI without ovarian stimulation followed by IVF and then EM (IUI without OS | IVF | EM)
iii. Clomifene citrate + IUI followed by IVF and then EM (CC + IUI | IVF | EM)
iv. Gonadatropins + IUI followed by IVF and then EM (Gn + IUI | IVF | EM)
v. Letrozole/anastrozole + IUI followed by IVF and then EM (nZole + IUI | IVF | EM)

The model is summarised below with full details available in appendix I.

A simple Markov approach was used to estimate cumulative live births from starting treatment to the end of a woman's reproductive life. In each monthly cycle women would either transition to a health state of "live birth" or remain in a "no birth" state as illustrated in Figure 17. The model accounted for the fact that woman who did not achieve live birth from assisted reproduction might do so through spontaneous conception.

Figure 17: Markov schematic to assess fertility treatments across a woman's reproductive life cycle

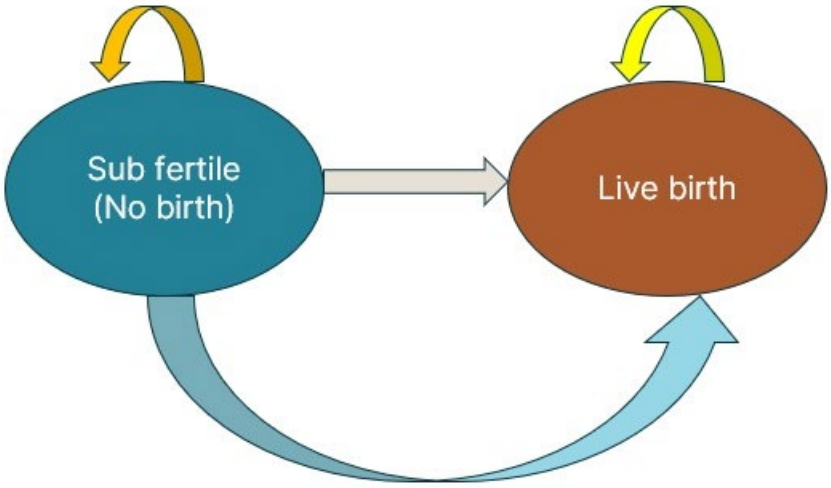
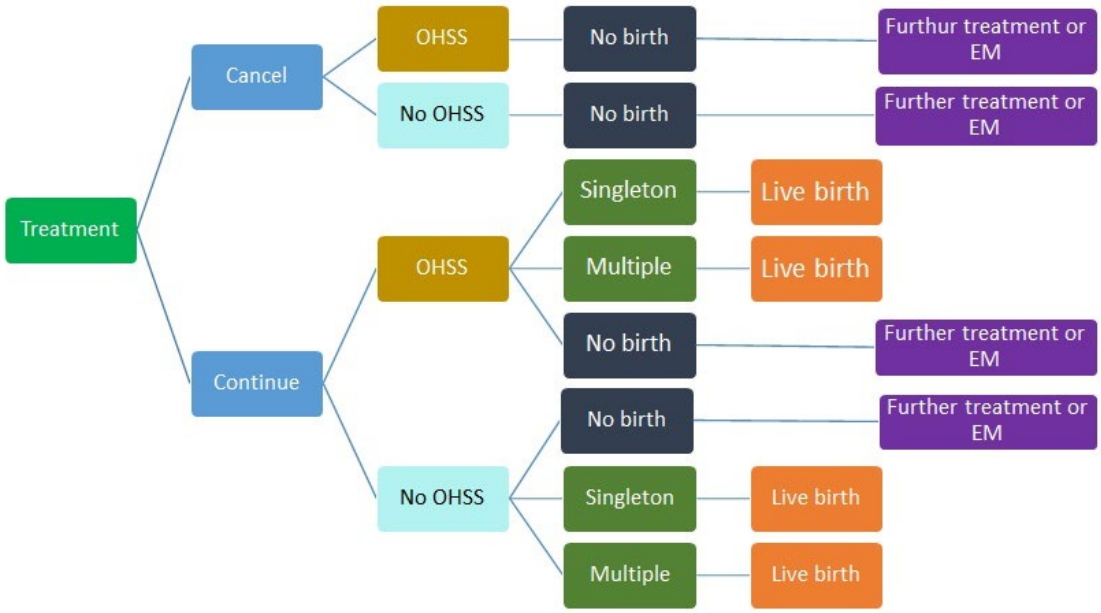


Figure 18 shows a schematic of the decision tree used to calculate the expected costs and outcomes associated with assisted reproduction.

Figure 18: Decision tree illustrating the outcomes of assisted reproduction



The model used relative treatment effects from the NMA to estimate live birth from assisted reproduction. These relative effects were applied to a baseline of no treatment (or EM) estimated from the van Eekelen prediction model. That same model was used to estimate live births arising from spontaneous conception following the completion of treatment. Published literature was used to estimate OHSS and multiple birth.

In addition to treatment costs the model also captured the “downstream” costs of multiple birth and OHSS associated with the different strategies. QALYs were estimated by assuming a health state utility gain from a live birth and then subtracting QALY losses from OHSS.

The results of the base case analysis suggested that IVF was the most cost-effective strategy. In a probabilistic sensitivity analysis IVF had the highest Net Monetary Benefit of £14,616 using a cost-effectiveness threshold of £30,000 per QALY. The analysis suggested that there was a 55% probability of IVF being the most cost-effective threshold of £30,000 per QALY, rising to 74% when a more restrictive £20,000 cost per QALY cost-effectiveness threshold was used. Gn + IUI | IVF was the most effective and most costly strategy but an ICER of £39,124 per QALY exceeded even the £30,000 per QALY threshold.

A number of sensitivity analyses were undertaken and in most of them IVF remained the most cost-effective strategy. However, the conclusion was particularly sensitive to the baseline birth rate and the health state utility gain from live birth. If a higher baseline birth rate or higher health state utility gain from live birth was assumed, then Gn + IUI was found to be the most cost-effective strategy at a cost-effectiveness threshold of £30,000 per QALY.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

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

Multiple gestation was also prioritised as a critical outcome and the primary safety outcome. There are a number of potential complications and difficulties associated with multiple gestation, and the risk of multiple gestation is increased when ovarian stimulation is used.

Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, and termination of pregnancy) was prioritised as an important outcome as it provides meaningful information about the success of a pregnancy and can have a significant impact on psychological and physical health. The committee also prioritised the rate of ovarian hyperstimulation syndrome (OHSS) as an important outcome as it is necessary when discussing and deciding on whether to undertake ovarian stimulation that risks are considered and weighed up against potential benefits.

The quality of the evidence

NMA

Most of the individual studies included in the NMAs were rated low or very low quality, mainly due to risk of bias stemming from poor reporting of randomisation procedures, failure to report intention-to-treat (ITT) analyses, or missing outcome data. This impacted on the quality of the NMAs.

The NMAs on clinical pregnancy, live birth and multiple pregnancy allowed estimation of relative effects between all pairs of treatments for people with unexplained fertility problems, via direct and indirect comparisons, using available RCT evidence. Fixed effect models were preferred (based on model fit) for the NMA for live birth in a mixed prognosis population and the NMA for multiple pregnancy in a poor prognosis population, where the network comprised of just one study on each arm. Random effect models were preferred for all other NMAs based on model fit, with considerable heterogeneity between studies.

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts and there should be no meaningful differences between these two sources of evidence. The consistency checks were undertaken by Technical Support Unit (University of Bristol) and are summarised in in Appendix N.

Inconsistency was only found for the full dataset NMA for the live birth outcome which was found to be due to both are of the two-armed Steures and Farquhar 2018 studies. If these studies were excluded, then a fixed effect model was preferred based on model fit statistics. Although the relative treatment effects remained largely unchanged after removing these studies, heterogeneity was substantially reduced with a corresponding reduction in credible intervals for all interventions. Whilst no studies were identified as inconsistent with the wider network for the full dataset clinical pregnancy NMA, excluding Steures 2006 and Farquhar 2018 did substantially reduce heterogeneity.

Threshold analysis on the live birth outcome (appendix M) suggested that the finding that IVF was the most effective treatment for increasing the odds of live birth was consistent when looking at the population without an explicitly poor prognosis (mixed) and when looking across the whole population: those with poor prognosis and those with any prognosis. Threshold analysis did reveal cases in which small changes in the findings of individual studies would change the optimal treatment from IVF to IUI with gonadotrophins (in the fixed-

effect NMA model of the population with mixed prognosis) or change the optimal treatment from IVF to IUI with clomifene citrate or gonadotrophins (in the random-effect NMA model of the population with any prognosis). However, the largely robust findings gave the committee confidence in the recommendations they made based on the NMA evidence.

Pairwise meta-analysis

The quality of the evidence for quantitative outcomes assessed in pairwise meta-analyses were assessed with GRADE methodology and the overall confidence in the findings was predominantly very low or low (with the exception of 1 high rating). Findings were downgraded due to risk of bias (arising from poor reporting of randomisation procedures, non-ITT analyses, and missing outcome data) and imprecision (95% confidence intervals crossed 1 or more decision-making thresholds).

See appendix F for full GRADE tables with quality ratings of all outcomes.

Benefits and harms

The committee discussed the network meta-analysis evidence on assisted reproduction techniques for people with unexplained fertility problems, mild endometriosis, and mild male factor fertility problems. They particularly focused on the NMAs on live birth for making recommendations as that was considered to be the most relevant and important measure of treatment effectiveness.

The committee noted that the very wide credible intervals for the odds ratios for assisted reproduction techniques relative to expectant management for all 3 NMAs undertaken for the live birth outcome which meant that conclusions about the relative treatment effect are very uncertain, reflecting the limitations and variation in the studies included in the NMA. Nevertheless, for the full population and mixed prognosis NMAs, the committee noted that IVF and gonadotropin or clomifene citrate plus IUI, had the highest odds ratios and were the only interventions which had credible intervals that did not cross the line of no effect. For the full dataset live birth NMA, IVF and gonadotropin or clomifene plus IUI had a 46% and 32% probability respectively of being the most effective treatment. In the mixed prognosis dataset, which excluded those studies restricted to poor prognosis patients only, IVF had an 80% probability of being the most effective treatment with the probability for gonadotropin plus IUI being most effective being 20%.

Therefore, the committee concluded that the NMAs provided good evidence on the clinical effectiveness of IVF and gonadotropin plus IUI even if the precise effect size was highly uncertain. The committee also appraised the NMA for live birth for those studies restricted to a poor prognosis population, as determined by prediction models. However, data was sparser in this NMA which was reflected in odds ratios with especially wide credible intervals. All the odds ratios for the poor prognosis group crossed the line of no effect and the committee therefore did not think it was appropriate to make any specific recommendations for the poor prognosis group.

Clinical pregnancy had been considered as a critical outcome as it is more commonly measured in research and is therefore can be a useful proxy for live birth, the real outcome of interest, especially if data on live births is limited. A broader range of interventions was included in the full dataset clinical pregnancy NMA and IVF had the greatest odds ratio relative to expectant management. The credible intervals for IVF also did not cross the ‘line of no effect’ indicating that increases in clinical pregnancy were unlikely to be due to chance. Two other treatments, clomifene citrate or gonadotropin plus IUI and gonadotropin with anastrozole or letrozole plus IUI, also had credible intervals suggestive of a real benefit of treatment in terms of clinical pregnancy. Whilst the committee were reassured that the results of the clinical pregnancy NMA was broadly consistent with that of the live birth NMA, it was not important in making recommendations in the context of the live birth treatment effects that were obtained.

Multiple pregnancy is usually considered as an adverse effect of assisted reproduction and therefore this was considered a critical outcome so that any benefits of assisted reproduction in terms of live birth could be weighed against the potential harms. The data for the NMA outcomes was particularly sparse with studies often having small denominators and sometimes zero events. Therefore, the multiple NMAs had very wide credible intervals and all treatments crossed the 'line of no effect'. The committee reflected that all assisted reproduction interventions would be expected to produce higher pregnancy rates than expectant management but even this was not clearly demonstrated in the odds ratio point estimates. However, the committee noted that the actual number of expectant management pregnancies in the dataset was very small and that the absolute number of multiple pregnancies in those pregnancies was considerably higher than is typically observed (5 multiple pregnancies across 114 expectant management pregnancies). Furthermore, some of the studies used for the multiple pregnancy outcome included direct evidence where there were more multiple births in the expectant arm and in one of these there were zero events in the comparator arms. Therefore, the committee did not think they could reasonably use the effectiveness data from the multiple birth pregnancy NMAs to inform recommendations.

Based on their knowledge and experience the committee believe that the effectiveness of IVF continues to improve over time as a result of technological improvements whereas the effectiveness of IUI is not expected to improve to the same extent. The committee believe that the NMA evidence is supportive of IVF as the most effective assisted reproductive technique for live birth but that it may underestimate its extent in the present day given the inevitable historical nature of the studies that informed the NMA.

The committee recognised that for the full live birth dataset it was clomifene or gonadotropin plus IUI intervention category rather than gonadotropin plus IUI which did not cross the line of no effect. However, they noted that the NMA produced a higher odds ratio for gonadotropin plus IUI than it did for clomifene plus IUI and that in the NMA for the mixed prognosis live birth dataset, clomifene plus IUI also did not cross the line of no effect. Therefore, the committee concluded that the evidence for gonadotropin plus IUI being an effective treatment for live birth was greater than it was for clomifene plus IUI.

Committee agreed that the evidence did not support the use of ovarian stimulation as a stand-alone treatment for people with unexplained fertility problems, mild endometriosis or mild male factor fertility problems. This is consistent with the previous guideline's (CG156) recommendations.

Finally, the committee considered the results of a threshold analysis. This suggested that there were cases where small changes in the findings of individual studies could lead to IUI with gonadotropin or clomifene in the any prognosis live birth NMA, or IUI with gonadotropin in the mixed prognosis live birth NMA, being the most effective treatment rather than IVF. Nevertheless, based on the overall NMA evidence and their clinical knowledge and experience, the committee reasoned that there was stronger evidence to support IVF on clinical effectiveness grounds, whilst recognising that cost effectiveness (see below) should inform their final recommendations.

Cost effectiveness and resource use

This topic area was identified as a high priority area for original health economic modelling as it was thought that new evidence meant that the NICE recommendation that IUI should not be routinely offered to people with unexplained infertility, mild endometriosis or 'mild male factor infertility' and who are having regular unprotected sexual intercourse should be revisited.

A systematic literature review identified 6 health economic evaluations for inclusion with all but one study being from a non-UK setting. Danhof 2020 and Van Eekelen 2021 compared the cost-effectiveness ovarian stimulation for agents, but the committee noted that did not address the bigger question with respect to the cost-effectiveness of IUI compared to other

assisted reproduction techniques. The guideline committee made a similar observation for the Bordewijk 2019 which assessed only ovarian stimulation (with or without IUI). Wordsworth 2011 was part of the health economic literature reviewed for the previous NICE guideline (NG156). This study using data from a published RCT (Bhattacharya 2008) concluded that IUI was a more expensive treatment than EM but did not offer statistically significant live birth rates and was therefore unlikely to represent a cost-effective use of NHS resources.

Tjon-Kon-Fat 2015 undertook an economic evaluation alongside an RCT (Bensdorp 2015) compared conventional IVF, modified natural cycle IVF and IUI. The authors concluded that IUI should be the first line treatment as all interventions had similar live birth rates, but that IUI was markedly cheaper and remarked that the NICE guideline (CG156) recommendation not to use IUI was unsustainable whilst agreeing that further research is required.

Finally van Eekelen 2020 was a Dutch study which used the results of an NMA to compare EM, IUI and IVF strategies. Their results suggested that a period of EM followed by first line IVF or EM followed by first line IUI then IVF second line were the most cost-effective policies whilst noting that precise conclusions depended on assumptions about the willingness to pay for a live birth. The committee agreed that this was the most useful study for making recommendations but an original model health economic model was developed which would also use an NMA undertaken for this guideline to provide estimates of clinical effectiveness.

This NMA provided the most up to date and best clinical evidence across a range of assisted reproduction techniques. The committee considered this economic analysis when making recommendations on assisted reproduction techniques for people with unexplained fertility problems, mild endometriosis, and mild male factor fertility problems the use of vaginal interventions to prevent or delay spontaneous preterm birth.

The committee noted that using IUI as a gateway treatment prior to IVF did not lead to lower costs overall, as IVF as a first line treatment was always the cheapest strategy, even in the sensitivity analysis where the costs of IVF were increased above their baseline value. This was because the success rates with first line IUI were not sufficiently high that the reduction in costs resulting from less patients needing IVF did not offset the costs of an additional treatment (IUI) being provided prior to IVF.

The committee recognised that in the base case analysis and in most sensitivity analyses that IVF was the most cost-effective treatment and that in most analyses this was accompanied with a high probability of that being the case. Therefore, the committee reasoned that it was reasonable to make a strong recommendation that IVF be offered as a first line treatment.

However, given the uncertainty around baseline spontaneous conception but especially the valuation of the gains from a live birth, the committee thought there was sufficient cost-effectiveness evidence to support a weaker recommendation to consider gonadotropin plus IUI as an alternative 1st line treatment, followed by IVF if unsuccessful.

The committee did not think the health economic evidence supported recommendations for IUI without ovarian stimulation or to use either clomiphene, letrozole or anastrozole as stimulation agents for IUI.

The committee did not think their recommendations would have a significant resource impact as the previous NICE guideline also recommended IVF as a first line treatment. However, the committee acknowledged that their permissive recommendation for IUI as a first line alternative could result in some increase in costs, but the committee believed this would be limited as they expected that it would only affect a small proportion of the relevant population and that it would avert the need for some women to have IVF.

1 Recommendations supported by this evidence review

2 This evidence review supports recommendations 1.8.2 and 1.8.3.

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Table 21: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023451142
1.	Review title	Clinical and cost effectiveness of assisted reproduction techniques for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter
2.	Review question	What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?
3.	Objective	To determine the clinical and cost effectiveness of assisted reproduction techniques for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter
4.	Searches	The following databases will be searched (from 2000 to the date of the search): Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by:

ID	Field	Content
		• 6English language • Human studies The guideline committee will decide whether and when to re-run the searches before final submission of the review to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Assisted reproduction techniques (ART) for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter
6.	Population	Inclusion: • People with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter Unexplained health-related fertility defined as no health-related impediment to fertility identified by standard investigations (including semen analysis, tubal patency tests, and assessment of ovulation), but pregnancy not achieved: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of assisted insemination. People with mild endometriosis (defined as American Society for Reproductive Medicine [rASRM] stage 1 or 2) would be eligible for inclusion but those with moderate or severe endometriosis would be excluded. Studies that include people with a single abnormal semen parameter (a single variable usually assessed in at least 2 analyses) would be eligible for inclusion (abnormal defined as a value below the 5th centile defined by the World Health Organization, 2021: semen volume 1.4ml; sperm concentration 16 × 106/mL; total sperm number 39 × 106 per ejaculate; total motility 42%; progressive motility 30%)

ID	Field	Content
		8Studies where participants are receiving first-line treatment at the point of randomisation will be included. If a study includes a number of cycles it will be eligible for inclusion assuming that participants are treatment naïve at baseline. However, studies that are restricted to further-line fertility treatment will be excluded. If some, but not all, of a study's participants are eligible for the review, for instance, mixed mild and moderate endometriosis, then we will include a study if at least 80% of its participants are eligible for this review.

7.	Intervention	Inclusion:
		• Ovarian stimulation using:
		  ○ clomifene citrate
		  ○ letrozole or anastrozole
		  ○ gonadotropins
		  ○ gonadotropin + clomifene citrate
		  ○ gonadotropin + (letrozole or anastrozole)
		• Intrauterine insemination (IUI) without ovarian stimulation
		• Intrauterine insemination with ovarian stimulation (IUI-OS):
		  ○ clomifene citrate + IUI
		  ○ letrozole or anastrozole + IUI
		  ○ gonadotropins + IUI
		  ○ (gonadotropin + clomifene citrate) + IUI
		  ○ (gonadotropin + (letrozole or anastrozole)) + IUI
		• IVF (without intracytoplasmic sperm injection [ICSI]):
		  ○ IVF with a single embryo transfer
		  ○ IVF with a double embryo transfer
		• Expectant management (including timed intercourse)
		
		Exclusion:
		• Fallopian tube sperm perfusion is not relevant to this review
		• Comparisons between stimulated and unstimulated IVF, or between different stimulation agents for IVF are not relevant for this review
		• Comparisons between types or lengths of luteal phase support are not relevant for this review

8.	Comparator	Trials comparing at least 2 of the above interventions

ID	Field	Content
9.	Types of study to be included	• RCTs* • Systematic reviews of RCTs (for identification of eligible studies) *Cross-over RCTs will be included but only where data can be extracted for the end of the first phase Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded
10.	Other exclusion criteria	Other exclusion criteria: • Language limitations: non-English-language papers will be excluded (unless data can be obtained, and risk of bias assessed, from an existing systematic review) • Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted (and risk of bias assessed) from elsewhere (for instance, from an existing systematic review)
11.	Context	This guidance will fully update the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
12.	Primary outcomes (critical outcomes)	• Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks; multiple births will be counted as 1 live birth event) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least 1 fetal heartbeat) • Multiple gestation (primary safety outcome; defined as an ultrasound scan that has shown at least 2 fetal heartbeats)
13.	Secondary outcomes (important outcomes)	• Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Ovarian Hyperstimulation Syndrome (OHSS)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. Data will be extracted into a standardised template created in Microsoft Excel, providing study reference, participant characteristics (including age, duration of infertility, body mass index, previous treatment [% treatment naïve], and primary/secondary infertility), intervention details, and outcome data. Data extraction will be double-coded.

ID	Field	Content
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the Cochrane RoB tool v.2. Risk of bias assessments will be double-coded. Threshold analysis will be conducted to assess the robustness of intervention recommendations due to bias (Phillippo 2018).
16.	Strategy for data synthesis	Network meta-analysis (NMA) in a Bayesian framework will be used to synthesise the data for all eligible interventions which are connected in a network of RCT comparisons for the primary outcomes. Dichotomous data (number of events) will be extracted from the studies and synthesised in the NMA. Results will be presented as log-odds ratios (LORs) with their corresponding 95% credible interval. An intention to treat (ITT) approach will be taken where possible. Where data is not available for all randomised participants, values will be imputed based on the assumption that the event did not occur in those with missing outcome data. Heterogeneity of studies, with regards to populations (particularly female age and duration of infertility) and methodologies, will be considered in order to assess the transitivity assumption. For the NMA it is assumed that any person that meets all inclusion criteria is, in principle, equally likely to be randomised to any of the interventions. The random class effects assumption will be assessed by comparing the fit of fixed and random class effects models, where the former assumes the intervention effects within each class are the same (i.e., no within-class variability of effects). The consistency of direct and indirect evidence will be assessed by fitting and comparing the fit of the NMA and unrelated mean effects (UME) models, the latter of which is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast (Dias 2011). Each data point's contribution to the posterior mean residual deviance for the NMA model will be plotted against that for the UME model, to visually assess if specific data points are contributing to inconsistency. If the UME suggests there is evidence of inconsistency, node-split models will be fitted to assist in identifying loops of evidence with inconsistency (Dias 2010). Where there is available data, separate pairwise analyses (outside of the NMA) will be conducted for secondary outcomes using Cochrane Review Manager software, and data will be presented as risk ratios or odds ratios (all included outcomes are dichotomous outcomes). It is considered likely that a fixed-effects model will be used for pairwise meta-analyses (based on the assumption that studies will be similar in terms of populations and interventions). Where there is serious or very serious heterogeneity (indicated by visual inspection of forest plots and an I-squared value of over 50% and 80% respectively), subgroup analyses (for age [female mean age ≥35 years and <35 years] and duration of infertility [≤2 years and >2 years]) will be conducted. Where heterogeneity cannot be accounted for by subgroup analyses, a random effects meta-analysis will be conducted (and both random effects and fixed effects analyses will be presented). If the fixed and random effect estimates differ, sensitivity analyses excluding small studies will be considered. If very serious heterogeneity remains, data will not be pooled across studies, and results will be summarised narratively.

ID	Field	Content	
17.	Analysis of sub-groups	If the network structure allows, sensitivity analyses will be considered, by excluding trials with a female mean age ≥35 years, and examining any differences in magnitude of effects and ranking.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify) Proportional (single-arm) meta-analysis
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	September 2023	
22.	Anticipated completion date	November 2024	
23.	Stage of review at time of this submission		

Review stage	Started	Completed
Preliminary searches	☐	☑
Piloting of the study selection process	☐	☑
Formal screening of search results against eligibility criteria	☐	☑
Data extraction	☐	☑
Risk of bias (quality) assessment	☐	☑
Data analysis	☐	☑

24.	Named contact	5a. Named contact

ID	Field	Content
		Guideline Development Team A 5b. Named contact e-mail FertilityProblems@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team A, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)
25.	Review team members	• Senior Technical Analyst • Technical Analyst
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023451142
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

ID	Field	Content	
		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Female factor fertility problems, infertility, ovarian reserve testing	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

ART: assisted reproductive techniques; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; IVF: in vitro fertilisation; LORs: log-odds ratios; MEDLINE: Medical Literature Analysis and Retrieval System Online; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; OHSS: Ovarian Hyperstimulation Syndrome; OS: ovarian stimulation; RCT: randomised controlled trial; UME: unrelated mean effects

Appendix B Literature search strategies

Literature search strategies for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Database: Ovid MEDLINE(R) ALL <1946 to September 07, 2023>

Date of last search: 08/09/2023

#	Searches
1	exp Infertility/
2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
3	Endometriosis/
4	endometrio*.tw.
5	sperm count/ or sperm motility/ or sperm transport/
6	((mild* or moderat*) adj4 male* factor*).tw.
7	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or sub-optimal* or deform* or weak* or inadequat* or sub-standard* or substandard*) adj2 (sperm* or semen*)).tw.
8	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
9	or/1-8
10	Reproductive Techniques, Assisted/
11	(((artificial* or assist*) adj2 (conception* or reproduct*)) or ART).tw.
12	exp ovulation induction/
13	(ovulat* adj2 (induc* or stimulat* or control* or time* or timing*)).tw.
14	(ovar* adj2 (stimulat* or induc* or hyperstimulat*)).tw.
15	(superovulat* or super ovulat*).tw.
16	(COS or COH).tw.
17	Gonadotropins/ or exp follicle stimulating hormone/
18	(gonadotrophin* or gonadotropi*).tw.
19	((follicle stimulating or folliculostimulating or folliculo-stimulating) adj2 hormone*).tw.
20	(FSH or rFSH or recFSH or uFSH or rhFSH or hpFSH or pFSH or follitropin or follitrophin or follitropine or follicotropin or folltropin or fertiline or fertinom or fertiline or anthrogon or puregon or metrodin or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17 or corifollitropin or elonva).tw.
21	exp menotropins/
22	(HMG or hMGhp or menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp89044 or cp-90033 or cp90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or org31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
23	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
24	selective estrogen receptor modulators/ or clomiphene/ or raloxifene hydrochloride/ or tamoxifen/
25	(anti-?estrogen* or anti?estrogen*).tw.
26	(SERMs or SERM).tw.
27	((?estrogen* or ?estradiol) adj3 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
28	(tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or clomiphen or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or trans-clomiphene or zuclomifene or dyneric or gravosan or klostilbegit or uclomiphene or raloxifene or evista or keoxifene or isomer).tw.
29	aromatase inhibitors/ or letrozole/
30	((aromatase adj2 (inhibit* or antagonist*)) or letrozole or femara or anastrozole).tw.
31	exp Insemination, Artificial/

#	Searches
32	(((artificial* or assist* or intrauter* or intra-uter*) adj2 inseminat*) or ICSI or IC SI or IUI).tw.
33	(eutelegenes?s or IUI or AIH).tw.
34	fertilization in vitro/ or sperm injections, intracytoplasmic/
35	(IVF or (in vitro fertili* or invitro fertili*)).tw.
36	((intracytoplasm* or intra cytoplasm* or microinject* or micro inject* or transfer*) adj2 sperm*).tw.
37	exp Embryo Transfer/
38	((embryo* or blastocyst*) adj2 (transfer* or transplant* or transport*)).tw.
39	Coitus/ or Watchful Waiting/
40	((active* adj1 surveill*) or (clinical adj1 observ*) or (expect* adj2 (approach* or manag*)) or "no intervention*" or "no therap*" or "no treatment*" or (without adj1 (intervention* or therap* or treatment*)) or (wait* adj1 see*) or (watch* adj2 wait*)).tw.
41	((coital or coitus or intercourse* or sex*) adj1 (frequen* or regular* or unprotect* or tim*)).tw.
42	(((artificial* or modifi* or natural*) adj3 cycle*) or NCIVF).tw.
43	or/10-42
44	9 and 43
45	letter/
46	editorial/
47	news/
48	exp historical article/
49	Anecdotes as topic/
50	comment/
51	case reports/
52	(letter or comment*).ti.
53	or/45-52
54	randomized controlled trial/ or random*.ti,ab.
55	53 not 54
56	animals/ not humans/
57	exp Animals, Laboratory/
58	exp Animal Experimentation/
59	exp Models, Animal/
60	exp Rodentia/
61	(rat or rats or rodent* or mouse or mice).ti.
62	or/55-61
63	44 not 62
64	limit 63 to english language
65	limit 64 to ed=20000101-20230908
66	limit 64 to dt=20000101-20230908
67	65 or 66
68	meta-analysis/
69	meta-analysis as topic/
70	(meta analy* or metanaly* or metaanaly*).ti,ab.
71	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
72	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
73	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
74	(search* adj4 literature).ab.
75	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
76	cochrane.jw.
77	or/68-76
78	randomized controlled trial.pt.
79	controlled clinical trial.pt.
80	pragmatic clinical trial.pt.
81	randomi#ed.ab.

#	Searches
82	placebo.ab.
83	randomly.ab.
84	Clinical Trials as topic.sh.
85	trial.ti.
86	or/78-85
87	67 and (77 or 86)

1 **Database: Embase <1974 to 2023 September 07>**

2 **Date of last search: 08/09/2023**

#	Searches
1	exp infertility/
2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
3	exp endometriosis/
4	endometrio*.tw.
5	semen parameters/ or exp sperm count/ or sperm quality/ or sperm viability/ or spermatozoon density/ or spermatozoon motility/ or spermatozoon migration/
6	semen abnormality/ or asthenospermia/ or cryptozoospermia/ or oligospermia/ or spermatozoon abnormality/
7	((mild* or moderat*) adj4 male* factor*).tw.
8	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or sub-optimal* or deform* or weak* or inadequat* or sub-standard* or substandard*) adj2 (sperm* or semen*)).tw.
9	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
10	or/1-9
11	infertility therapy/
12	(((artificial* or assist*) adj2 (conception* or reproduct*)) or ART).tw.
13	ovulation induction/
14	(ovulat* adj2 (induc* or stimulat* or control* or time* or timing*)).tw.
15	(ovar* adj2 (stimulat* or induc* or hyperstimulat*)).tw.
16	(superovulat* or super ovulat*).tw.
17	(COS or COH).tw.
18	gonadotropin/ or gonadotrophin derivative/ or exp follitropin derivative/
19	(gonadotrophin* or gonadotropi*).tw.
20	((follicle stimulating or folliculostimulating or folliculo-stimulating) adj2 hormone*).tw.
21	(FSH or rFSH or recFSH or uFSH or rhFSH or hpFSH or pFSH or follitropin or follitrophin or follitropine or follicotropin or folltropin or fertiline or fertinom or fertiline or anthrogon or puregon or metrodin or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17 or corifollitropin or elonva).tw.
22	human menopausal gonadotropin/
23	(HMG or hMGhp or menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp89044 or cp-90033 or cp90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or org31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
24	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
25	exp antiestrogen/
26	(anti-?estrogen* or anti?estrogen*).tw.
27	(SERMs or SERM).tw.
28	((?estrogen* or ?estradiol) adj3 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
29	(tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or clomiphen or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or trans-clomiphene or zuclomifene or dyneric or gravosan or klostilbegit or uclomiphene or raloxifene or evista or keoxifene or isomer).tw.
30	exp aromatase inhibitor/
31	((aromatase adj2 (inhibit* or antagonist*)) or letrozole or femara or anastrozole).tw.

#	Searches
32	exp artificial insemination/
33	(((artificial* or assist* or intrauter* or intra-uter*) adj2 inseminat*) or ICSI or IC SI or IUI).tw.
34	(eutelegenes?s or IUI or AIH).tw.
35	in vitro fertilization/
36	intracytoplasmic sperm injection/
37	(IVF or (in vitro fertili* or invitro fertili*)).tw.
38	((intracytoplasm* or intra cytoplasm* or microinject* or micro inject* or transfer*) adj2 sperm*).tw.
39	exp embryo transfer/
40	((embryo* or blastocyst*) adj2 (transfer* or transplant* or transport*)).tw.
41	coitus/ or sexual intercourse/
42	watchful waiting/
43	((active* adj1 surveill*) or (clinical adj1 observ*) or (expect* adj2 (approach* or manag*)) or "no intervention*" or "no therap*" or "no treatment*" or (without adj1 (intervention* or therap* or treatment*)) or (wait* adj1 see*) or (watch* adj2 wait*)).tw.
44	((coital or coitus or intercourse* or sex*) adj1 (frequen* or regular* or unprotect* or tim*)).tw.
45	(((artificial* or modifi* or natural*) adj3 cycle*) or NCIVF).tw.
46	or/11-45
47	10 and 46
48	letter.pt. or letter/
49	note.pt.
50	editorial.pt.
51	case report/ or case study/
52	(letter or comment*).ti.
53	or/48-52
54	randomized controlled trial/ or random*.ti,ab.
55	53 not 54
56	animal/ not human/
57	nonhuman/
58	exp Animal Experiment/
59	exp Experimental Animal/
60	animal model/
61	exp Rodent/
62	(rat or rats or rodent* or mouse or mice).ti.
63	or/55-62
64	47 not 63
65	limit 64 to english language
66	limit 65 to dc=20000101-20230908
67	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
68	66 not 67
69	systematic review/
70	meta-analysis/
71	(meta analy* or metanaly* or metaanaly*).ti,ab.
72	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
73	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75	(search* adj4 literature).ab.
76	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
77	((pool* or combined) adj2 (data or trials or studies or results)).ab.
78	cochrane.jw.
79	or/69-78
80	random*.ti,ab.
81	factorial*.ti,ab.

#	Searches
82	(crossover* or cross over*).ti,ab.
83	((doubl* or singl*) adj blind*).ti,ab.
84	(assign* or allocat* or volunteer* or placebo*).ti,ab.
85	crossover procedure/
86	single blind procedure/
87	randomized controlled trial/
88	double blind procedure/
89	or/80-88
90	68 and (79 or 89)

1 **Database: Cochrane Database of Systematic Reviews Issue 9 of 12, September 2023**

2 **Date of last search: 08/09/2023**

#	Searches
#1	MeSH descriptor: [Infertility] explode all trees
#2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*):ti,ab
#3	MeSH descriptor: [Endometriosis] this term only
#4	endometrio*:ti,ab
#5	MeSH descriptor: [Sperm Count] this term only
#6	MeSH descriptor: [Sperm Motility] this term only
#7	MeSH descriptor: [Sperm Transport] this term only
#8	((mild* or moderat*) near/4 (male* next factor*)):ti,ab
#9	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or sub-optimal* or deform* or weak* or inadequat* or sub-standard* or substandard*) near/2 (sperm* or semen*)):ti,ab
#10	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*):ti,ab
#11	{or #1-#10}
#12	MeSH descriptor: [Reproductive Techniques, Assisted] this term only
#13	(((artificial* or assist*) near/2 (conception* or reproduct*)) or ART):ti,ab
#14	MeSH descriptor: [Ovulation Induction] explode all trees
#15	(ovulat* near/2 (induc* or stimulat* or control* or time* or timing*)):ti,ab
#16	(ovar* near/2 (stimulat* or induc* or hyperstimulat*)):ti,ab
#17	(superovulat* or (super next ovulat*)):ti,ab
#18	(COS or COH):ti,ab
#19	MeSH descriptor: [Gonadotropins] this term only
#20	MeSH descriptor: [Follicle Stimulating Hormone] explode all trees
#21	(gonadotrophin* or gonadotropi*):ti,ab
#22	(((follicle next stimulating) or folliculostimulating or folliculo-stimulating) near/2 hormone*):ti,ab
#23	(FSH or rFSH or recFSH or uFSH or rhFSH or hpFSH or pFSH or follitropin or follitrophin or follitropine or follicotropin or folltropin or fertiline or fertinom or fertiline or anthrogon or puregon or metrodin or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17 or corifollitropin or elonva):ti,ab
#24	MeSH descriptor: [Menotropins] explode all trees
#25	(HMG or hMGhp or menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp89044 or cp-90033 or cp90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or org31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex):ti,ab
#26	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon):ti,ab
#27	MeSH descriptor: [Selective Estrogen Receptor Modulators] this term only
#28	MeSH descriptor: [Clomiphene] this term only
#29	MeSH descriptor: [Raloxifene Hydrochloride] this term only
#30	MeSH descriptor: [Tamoxifen] this term only

#	Searches
#31	(anti-oestrogen* or anti-estrogen* or antioestrogen* or antiestrogen*):ti,ab
#32	(SERMs or SERM):ti,ab
#33	((oestrogen* or estrogen* or estradiol or oestradiol) near/3 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)):ti,ab
#34	(tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or clomiphen or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or trans-clomiphene or zuclomifene or dyneric or gravosan or klostilbegit or uclomiphene or raloxifene or evista or keoxifene or isomer):ti,ab
#35	MeSH descriptor: [Aromatase Inhibitors] this term only
#36	MeSH descriptor: [Letrozole] this term only
#37	((aromatase near/2 (inhibit* or antagonist*)) or letrozole or femara or anastrozole):ti,ab
#38	MeSH descriptor: [Insemination, Artificial] explode all trees
#39	(((artificial* or assist* or intrauter* or intra-uter*) near/2 inseminat*) or ICSI or "IC SI" or IUI):ti,ab
#40	(eutelegeneses or eutelegenesis or IUI or AIH):ti,ab
#41	MeSH descriptor: [Fertilization in Vitro] this term only
#42	MeSH descriptor: [Sperm Injections, Intracytoplasmic] this term only
#43	(IVF or ((in next vitro next fertili*) or (invitro next fertili*))):ti,ab
#44	((intracytoplasm* or (intra next cytoplasm*) or microinject* or (micro next inject*) or transfer*) near/2 sperm*):ti,ab
#45	MeSH descriptor: [Embryo Transfer] explode all trees
#46	((embryo* or blastocyst*) near/2 (transfer* or transplant* or transport*)):ti,ab
#47	MeSH descriptor: [Coitus] this term only
#48	MeSH descriptor: [Watchful Waiting] this term only
#49	((active* near/1 surveill*) or (clinical near/1 observ*) or (expect* near/2 (approach* or manag*)) or (no next intervention*) or (no next therap*) or (no next treatment*) or (without near/1 (intervention* or therap* or treatment*)) or (wait* near/1 see*) or (watch* near/2 wait*)):ti,ab
#50	((coital or coitus or intercourse* or sex*) near/1 (frequen* or regular* or unprotect* or tim*)):ti,ab
#51	(((artificial* or modifi* or natural*) near/3 cycle*) or NCIVF):ti,ab
#52	{or #12-#51}
#53	#11 and #52
#54	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#55	#53 not #54
#56	"conference":pt
#57	#55 not #56 with Cochrane Library publication date Between Jan 2000 and Sep 2023, in Cochrane Reviews

1 **Database: Cochrane Central Register of Controlled Trials Issue 8 of 12, August 2023**

2 **Date of last search: 08/09/2023**

#	Searches
#1	MeSH descriptor: [Infertility] explode all trees
#2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*):ti,ab
#3	MeSH descriptor: [Endometriosis] this term only
#4	endometrio*:ti,ab
#5	MeSH descriptor: [Sperm Count] this term only
#6	MeSH descriptor: [Sperm Motility] this term only
#7	MeSH descriptor: [Sperm Transport] this term only
#8	((mild* or moderat*) near/4 (male* next factor*)):ti,ab
#9	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or sub-optimal* or deform* or weak* or inadequat* or sub-standard* or substandard*) near/2 (sperm* or semen*)):ti,ab
#10	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*):ti,ab

#	Searches
#11	{or #1-#10}
#12	MeSH descriptor: [Reproductive Techniques, Assisted] this term only
#13	(((artificial* or assist*) near/2 (conception* or reproduct*)) or ART):ti,ab
#14	MeSH descriptor: [Ovulation Induction] explode all trees
#15	(ovulat* near/2 (induc* or stimulat* or control* or time* or timing*)):ti,ab
#16	(ovar* near/2 (stimulat* or induc* or hyperstimulat*)):ti,ab
#17	(superovulat* or (super next ovulat*)):ti,ab
#18	(COS or COH):ti,ab
#19	MeSH descriptor: [Gonadotropins] this term only
#20	MeSH descriptor: [Follicle Stimulating Hormone] explode all trees
#21	(gonadotrophin* or gonadotropi*):ti,ab
#22	(((follicle next stimulating) or folliculostimulating or folliculo-stimulating) near/2 hormone*):ti,ab
#23	(FSH or rFSH or recFSH or uFSH or rhFSH or hpFSH or pFSH or follitropin or follitrophin or follitropine or follicotropin or folltropin or fertiline or fertinom or fertiline or anthrogon or puregon or metrodin or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17 or corifollitropin or elonva):ti,ab
#24	MeSH descriptor: [Menotropins] explode all trees
#25	(HMG or hMGhp or menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp89044 or cp-90033 or cp90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or org31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex):ti,ab
#26	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon):ti,ab
#27	MeSH descriptor: [Selective Estrogen Receptor Modulators] this term only
#28	MeSH descriptor: [Clomiphene] this term only
#29	MeSH descriptor: [Raloxifene Hydrochloride] this term only
#30	MeSH descriptor: [Tamoxifen] this term only
#31	(anti-oestrogen* or anti-estrogen* or antioestrogen* or antiestrogen*):ti,ab
#32	(SERMs or SERM):ti,ab
#33	((oestrogen* or estrogen* or estradiol or oestradiol) near/3 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)):ti,ab
#34	(tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or clomiphen or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or trans-clomiphene or zuclomifene or dyneric or gravosan or klostilbegit or uclomiphene or raloxifene or evista or keoxifene or isomer):ti,ab
#35	MeSH descriptor: [Aromatase Inhibitors] this term only
#36	MeSH descriptor: [Letrozole] this term only
#37	((aromatase near/2 (inhibit* or antagonist*)) or letrozole or femara or anastrozole):ti,ab
#38	MeSH descriptor: [Insemination, Artificial] explode all trees
#39	(((artificial* or assist* or intrauter* or intra-uter*) near/2 inseminat*) or ICSI or "IC SI" or IUI):ti,ab
#40	(eutelegeneses or eutelegenesis or IUI or AIH):ti,ab
#41	MeSH descriptor: [Fertilization in Vitro] this term only
#42	MeSH descriptor: [Sperm Injections, Intracytoplasmic] this term only
#43	(IVF or ((in next vitro next fertili*) or (invitro next fertili*))):ti,ab
#44	((intracytoplasm* or (intra next cytoplasm*) or microinject* or (micro next inject*) or transfer*) near/2 sperm*):ti,ab
#45	MeSH descriptor: [Embryo Transfer] explode all trees
#46	((embryo* or blastocyst*) near/2 (transfer* or transplant* or transport*)):ti,ab
#47	MeSH descriptor: [Coitus] this term only
#48	MeSH descriptor: [Watchful Waiting] this term only
#49	((active* near/1 surveill*) or (clinical near/1 observ*) or (expect* near/2 (approach* or manag*)) or (no next intervention*) or (no next therap*) or (no next treatment*) or (without near/1 (intervention* or therap* or treatment*)) or (wait* near/1 see*) or (watch* near/2 wait*)):ti,ab
#50	((coital or coitus or intercourse* or sex*) near/1 (frequen* or regular* or unprotect* or tim*)):ti,ab
#51	(((artificial* or modifi* or natural*) near/3 cycle*) or NCIVF):ti,ab
#52	{or #12-#51}

#	Searches
#53	#11 and #52
#54	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#55	#53 not #54
#56	"conference":pt
#57	#55 not #56 with Publication Year from 2000 to 2023, in Trials

1

2 **Database: Epistemonikos – search 1**

3 **Date of last search: 08/09/2023**

#	Searches
1	(steril* OR sub-fertil* OR "sub fertility" OR "sub fertile" OR subfertil* OR infertil* OR infecund* OR sub-fecund* OR "sub fecundity" OR subfecund* OR hypofertil* OR endometrio* OR ((mild* OR moderat*) AND (male* AND factor*)) OR ((abnormal* OR block* OR defect* OR deficien* OR fail* OR immobil* OR immotil* OR impair* OR insufficien* OR low* OR reduc* OR suboptimal* OR sub-optimal* OR "sub optimal" OR "sub optimally" OR deform* OR weak* OR inadequat* OR sub-standard* OR "sub standard" OR substandard*) AND (sperm* OR semen*)) OR asthenospermi* OR asthenoteratozoospermi* OR asthenozoospermi* OR cryptozoospermi* OR cryptospermi* OR globozoospermi* OR hypospermatogen* OR oligospermi* OR oligozoospermi* OR teratospermi* OR teratozoospermi*)
	AND
2	(((artificial* OR assist*) AND (conception* OR reproduct*)) OR ART OR (ovulat* AND (induc* OR stimulat* OR control* OR time* OR timing*)) OR (ovar* AND (stimulat* OR induc* OR hyperstimulat*)) OR superovulat* OR (super AND ovulat*) OR COS OR COH OR gonadotrophin* OR gonadotropi* OR (("follicle stimulating" OR folliculostimulating OR folliculo-stimulating) AND hormone*) OR FSH OR rFSH OR recFSH OR uFSH OR rhFSH OR hpFSH OR pFSH OR follitropin OR follitrophin OR follitropine OR follicotropin OR folltropin OR fertiline OR fertinom OR fertiline OR anthrogon OR puregon OR metrodin OR afolia OR bemfola OR da-3801 OR "da 3801" OR da3801 OR “fe-999049” OR "fe 999049" OR fe999049 OR fertavid OR folitime OR follistim OR fostirel OR gonadopin OR gonal-f OR "gonal f" OR lm-00 OR "lm 00" OR lm001 OR org-32489 OR "org 32489" OR org32489 OR ovaleap OR primapur OR recagon OR rekovelle OR sj-0021 OR "sj 0021" OR sj0021 OR xm-17 OR "xm 17" OR xm17 OR corifollitropin OR elonva OR HMG OR hMGhp OR menotrop* OR "61489-71-2" OR "8049-76-1" OR "97048-13-0" OR “cp-89044” OR cp89044 OR “cp-90033” OR "cp 90033" OR cp90033 OR humegon OR humergon OR menogon OR menopur OR normegon OR “org-31338” OR "org 31338" OR org31338 OR pergonal OR neopergonal OR homogonal OR gonadoryl OR meriofert OR merional OR normegon OR “preg-norm” OR "preg norm" OR pregova OR repronex OR urofollitrop* OR metrodine OR metrodin OR fostimon OR follitrin OR follimon OR follegon OR fertinorm OR fertinex OR bravelle OR altermon)
3	1 AND 2
4	Limit to Systematic Reviews, Date 2000-2023

4 **Database: Epistemonikos – search 2**

5 **Date of last search: 08/09/2023**

#	Searches
1	(steril* OR sub-fertil* OR "sub fertility" OR "sub fertile" OR subfertil* OR infertil* OR infecund* OR sub-fecund* OR "sub fecundity" OR subfecund* OR hypofertil* OR endometrio* OR ((mild* OR moderat*) AND (male* AND factor*)) OR ((abnormal* OR block* OR defect* OR deficien* OR fail* OR immobil* OR immotil* OR impair* OR insufficien* OR low* OR reduc* OR suboptimal* OR sub-optimal* OR "sub optimal" OR "sub optimally" OR deform* OR weak* OR inadequat* OR sub-standard* OR "sub standard" OR substandard*) AND (sperm* OR semen*)) OR asthenospermi* OR asthenoteratozoospermi* OR asthenozoospermi* OR cryptozoospermi* OR cryptospermi* OR globozoospermi* OR hypospermatogen* OR oligospermi* OR oligozoospermi* OR teratospermi* OR teratozoospermi*)
	AND
2	(anti-oestrogen* OR "anti oestrogen" OR "anti oestrogens" OR "anti oestrogenic" OR anti-estrogen* OR antioestrogen* OR "anti estrogen" OR "anti estrogens" OR "anti estrogenic" OR antiestrogen* OR SERMs OR SERM OR ((oestrogen* OR estrogen* OR estradiol OR oestradiol) AND (modulator* OR inhibitor* OR antagonist* OR blocker* OR suppress*)) OR tamoxifen OR fulvestrant OR faslodex OR toremifene OR fareston OR nolvadex OR novaldex OR soltamox OR tomaxithen OR zitazonium OR clomifene OR clomid OR androxal OR clomiphene OR clomiphen OR chloramiphene OR clomide OR clomifen OR clostilbegit OR clostilbegyt OR enclomid OR enclomifene OR enclomiphen* OR serophene OR “trans-clomiphene” OR "trans clomiphene" OR zuclomifene OR dyneric OR gravosan OR klostilbegit OR uclomiphene OR raloxifene OR evista OR keoxifene OR isomer OR (aromatase AND (inhibit* OR antagonist*)) OR letrozole OR femara OR anastrozole)
3	1 AND 2
4	Limit to Systematic Reviews, Date 2000-2023

Database: Epistemonikos – search 3

Date of last search: 08/09/2023

#	Searches
1	(steril* OR sub-fertil* OR "sub fertility" OR "sub fertile" OR subfertil* OR infertil* OR infecund* OR sub-fecund* OR "sub fecundity" OR subfecund* OR hypofertil* OR endometrio* OR ((mild* OR moderat*) AND (male* AND factor*)) OR ((abnormal* OR block* OR defect* OR deficien* OR fail* OR immobil* OR immotil* OR impair* OR insufficien* OR low* OR reduc* OR suboptimal* OR sub-optimal* OR "sub optimal" OR "sub optimally" OR deform* OR weak* OR inadequat* OR "sub-standard" OR "sub standard" OR substandard*) AND (sperm* OR semen*)) OR asthenospermi* OR asthenoteratozoospermi* OR asthenozoospermi* OR cryptozoospermi* OR cryptospermi* OR globozoospermi* OR hypospermatogen* OR oligospermi* OR oligozoospermi* OR teratospermi* OR teratozoospermi*)
	AND
2	(((artificial* OR assist* OR intrauter* OR intra-uter* OR "intra uteral" OR "intra uterine" OR "intra uterus") AND inseminat*) OR ICSI OR "IC SI" OR IUI OR eutelegeneses OR eutelegenesis OR IUI OR AIH OR IVF OR "in vitro fertilization" OR "in vitro fertilisation" OR "invitro fertilization" OR "invitro fertilisation" OR (intracytoplasm* OR "intra cytoplasm" OR "intra cytoplasmic" OR microinject* OR "micro injection" OR "micro injected" OR transfer*) AND sperm*) OR ((embryo* OR blastocyst*) AND (transfer* OR transplant* OR transport*)) OR ((active* AND surveill*) OR (clinical AND observ*) OR (expect* AND (approach* OR manag*)) OR "no intervention" OR "no interventions" OR "no therapy" OR "no therapies" OR "no therapeutic" OR "no treatment" OR "no treatments" OR (without AND (intervention* OR therap* OR treatment*)) OR (wait* AND see*) OR (watch* AND wait*) OR ((coital OR coitus OR intercourse* OR sex*) AND (frequen* OR regular* OR unprotect* OR tim*)) OR ((artificial* OR modifi* OR natural*) AND cycle*) OR NCIVF)
3	1 AND 2
4	Limit to Systematic Reviews, Date 2000-2023

Health Economic Literature Search Strategies

Database: Ovid MEDLINE(R) ALL <1946 to September 15, 2023>

Date of last search: 18/09/2023

#	Searches
1	exp Infertility/
2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
3	Endometriosis/
4	endometrio*.tw.
5	sperm count/ or sperm motility/ or sperm transport/
6	((mild* or moderat*) adj4 male* factor*).tw.
7	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or sub-optimal* or deform* or weak* or inadequat* or sub-standard* or substandard*) adj2 (sperm* or semen*)).tw.
8	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
9	or/1-8
10	Reproductive Techniques, Assisted/
11	(((artificial* or assist*) adj2 (conception* or reproduct*)) or ART).tw.
12	exp ovulation induction/
13	(ovulat* adj2 (induc* or stimulat* or control* or time* or timing*)).tw.
14	(ovar* adj2 (stimulat* or induc* or hyperstimulat*)).tw.
15	(superovulat* or super ovulat*).tw.
16	(COS or COH).tw.
17	Gonadotropins/ or exp follicle stimulating hormone/
18	(gonadotrophin* or gonadotropi*).tw.
19	((follicle stimulating or folliculostimulating or folliculo-stimulating) adj2 hormone*).tw.
20	(FSH or rFSH or recFSH or uFSH or rhFSH or hpFSH or pFSH or follitropin or follitrophin or follitropine or follicotropin or folltropin or fertiline or fertinom or fertiline or anthrogon or puregon or metrodin or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17 or corifollitropin or elonva).tw.
21	exp menotropins/

#	Searches
22	(HMG or hMGhp or menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp89044 or cp-90033 or cp90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or org31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
23	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
24	selective estrogen receptor modulators/ or clomiphene/ or raloxifene hydrochloride/ or tamoxifen/
25	(anti-?estrogen* or anti?estrogen*).tw.
26	(SERMs or SERM).tw.
27	((?estrogen* or ?estradiol) adj3 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
28	(tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or clomiphen or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or trans-clomiphene or zuclomifene or dyneric or gravosan or klostilbegit or uclomiphene or raloxifene or evista or keoxifene or isomer).tw.
29	aromatase inhibitors/ or letrozole/
30	((aromatase adj2 (inhibit* or antagonist*)) or letrozole or femara or anastrozole).tw.
31	exp Insemination, Artificial/
32	(((artificial* or assist* or intrauter* or intra-uter*) adj2 inseminat*) or ICSI or IC SI or IUI).tw.
33	(eutelegenes?s or IUI or AIH).tw.
34	fertilization in vitro/ or sperm injections, intracytoplasmic/
35	(IVF or (in vitro fertili* or invitro fertili*)).tw.
36	((intracytoplasm* or intra cytoplasm* or microinject* or micro inject* or transfer*) adj2 sperm*).tw.
37	exp Embryo Transfer/
38	((embryo* or blastocyst*) adj2 (transfer* or transplant* or transport*)).tw.
39	Coitus/ or Watchful Waiting/
40	((active* adj1 surveill*) or (clinical adj1 observ*) or (expect* adj2 (approach* or manag*)) or "no intervention*" or "no therap*" or "no treatment*" or (without adj1 (intervention* or therap* or treatment*)) or (wait* adj1 see*) or (watch* adj2 wait*)).tw.
41	((coital or coitus or intercourse* or sex*) adj1 (frequen* or regular* or unprotect* or tim*)).tw.
42	(((artificial* or modifi* or natural*) adj3 cycle*) or NCIVF).tw.
43	or/10-42
44	9 and 43
45	letter/
46	editorial/
47	news/
48	exp historical article/
49	Anecdotes as topic/
50	comment/
51	case reports/
52	(letter or comment*).ti.
53	or/45-52
54	randomized controlled trial/ or random*.ti,ab.
55	53 not 54
56	animals/ not humans/
57	exp Animals, Laboratory/
58	exp Animal Experimentation/
59	exp Models, Animal/
60	exp Rodentia/
61	(rat or rats or rodent* or mouse or mice).ti.
62	or/55-61
63	44 not 62
64	limit 63 to english language
65	limit 64 to ed=20000101-20230930
66	limit 64 to dt=20000101-20230930
67	65 or 66

#	Searches
68	Economics/
69	Value of life/
70	exp "Costs and Cost Analysis"/
71	exp Economics, Hospital/
72	exp Economics, Medical/
73	exp Resource Allocation/
74	Economics, Nursing/
75	Economics, Pharmaceutical/
76	exp "Fees and Charges"/
77	exp Budgets/
78	budget*.ti,ab.
79	cost*.ti,ab.
80	(economic* or pharmaco?economic*).ti,ab.
81	(price* or pricing*).ti,ab.
82	(financ* or fee or fees or expenditure* or saving*).ti,ab.
83	(value adj2 (money or monetary)).ti,ab.
84	resourc* allocat*.ti,ab.
85	(fund or funds or funding* or funded).ti,ab.
86	(ration or rations or rationing* or rationed).ti,ab.
87	ec.fs.
88	or/68-87
89	quality-adjusted life years/
90	sickness impact profile/
91	(quality adj2 (wellbeing or well being)).ti,ab.
92	sickness impact profile.ti,ab.
93	disability adjusted life.ti,ab.
94	(qal* or qtime* or qwb* or daly*).ti,ab.
95	(euroqol* or eq5d* or eq 5*).ti,ab.
96	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
97	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
98	(hui or hui1 or hui2 or hui3).ti,ab.
99	(health* year* equivalent* or hye or hyes).ti,ab.
100	discrete choice*.ti,ab.
101	rosser.ti,ab.
102	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
103	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
104	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
105	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
106	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
107	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
108	or/89-107
109	67 and (88 or 108)

1 **Database: Embase <1974 to 2023 September 15>**

2 **Date of last search: 18/09/2023**

#	Searches
1	exp infertility/
2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
3	exp endometriosis/
4	endometrio*.tw.
5	semen parameters/ or exp sperm count/ or sperm quality/ or sperm viability/ or spermatozoon density/ or spermatozoon motility/ or spermatozoon migration/

#	Searches
6	semen abnormality/ or asthenospermia/ or cryptozoospermia/ or oligospermia/ or spermatozoon abnormality/
7	((mild* or moderat*) adj4 male* factor*).tw.
8	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or sub-optimal* or deform* or weak* or inadequat* or sub-standard* or substandard*) adj2 (sperm* or semen*)).tw.
9	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*).tw.
10	or/1-9
11	infertility therapy/
12	(((artificial* or assist*) adj2 (conception* or reproduct*)) or ART).tw.
13	ovulation induction/
14	(ovulat* adj2 (induc* or stimulat* or control* or time* or timing*)).tw.
15	(ovar* adj2 (stimulat* or induc* or hyperstimulat*)).tw.
16	(superovulat* or super ovulat*).tw.
17	(COS or COH).tw.
18	gonadotropin/ or gonadotrophin derivative/ or exp follitropin derivative/
19	(gonadotrophin* or gonadotropi*).tw.
20	((follicle stimulating or folliculostimulating or folliculo-stimulating) adj2 hormone*).tw.
21	(FSH or rFSH or recFSH or uFSH or rhFSH or hpFSH or pFSH or follitropin or follitrophin or follitropine or follicotropin or folltropin or fertiline or fertinom or fertiline or anthrogon or puregon or metrodin or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17 or corifollitropin or elonva).tw.
22	human menopausal gonadotropin/
23	(HMG or hMGhp or menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp89044 or cp-90033 or cp90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or org31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex).tw.
24	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon).tw.
25	exp antiestrogen/
26	(anti-?estrogen* or anti?estrogen*).tw.
27	(SERMs or SERM).tw.
28	((?estrogen* or ?estradiol) adj3 (modulator* or inhibitor* or antagonist* or blocker* or suppress*)).tw.
29	(tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or clomiphen or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or trans-clomiphene or zuclomifene or dyneric or gravosan or klostilbegit or uclomiphene or raloxifene or evista or keoxifene or isomer).tw.
30	exp aromatase inhibitor/
31	((aromatase adj2 (inhibit* or antagonist*)) or letrozole or femara or anastrozole).tw.
32	exp artificial insemination/
33	(((artificial* or assist* or intrauter* or intra-uter*) adj2 inseminat*) or ICSI or IC SI or IUI).tw.
34	(eutelegenes?s or IUI or AIH).tw.
35	in vitro fertilization/
36	intracytoplasmic sperm injection/
37	(IVF or (in vitro fertili* or invitro fertili*)).tw.
38	((intracytoplasm* or intra cytoplasm* or microinject* or micro inject* or transfer*) adj2 sperm*).tw.
39	exp embryo transfer/
40	((embryo* or blastocyst*) adj2 (transfer* or transplant* or transport*)).tw.
41	coitus/ or sexual intercourse/
42	watchful waiting/
43	((active* adj1 surveill*) or (clinical adj1 observ*) or (expect* adj2 (approach* or manag*)) or "no intervention*" or "no therap*" or "no treatment*" or (without adj1 (intervention* or therap* or treatment*)) or (wait* adj1 see*) or (watch* adj2 wait*)).tw.
44	((coital or coitus or intercourse* or sex*) adj1 (frequen* or regular* or unprotect* or tim*)).tw.
45	(((artificial* or modifi* or natural*) adj3 cycle*) or NCIVF).tw.
46	or/11-45

#	Searches
47	10 and 46
48	letter.pt. or letter/
49	note.pt.
50	editorial.pt.
51	case report/ or case study/
52	(letter or comment*).ti.
53	or/48-52
54	randomized controlled trial/ or random*.ti,ab.
55	53 not 54
56	animal/ not human/
57	nonhuman/
58	exp Animal Experiment/
59	exp Experimental Animal/
60	animal model/
61	exp Rodent/
62	(rat or rats or rodent* or mouse or mice).ti.
63	or/55-62
64	47 not 63
65	limit 64 to english language
66	limit 65 to dc=20000101-20230930
67	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
68	66 not 67
69	health economics/
70	exp economic evaluation/
71	exp health care cost/
72	exp fee/
73	budget/
74	funding/
75	resource allocation/
76	budget*.ti,ab.
77	cost*.ti,ab.
78	(economic* or pharmaco?economic*).ti,ab.
79	(price* or pricing*).ti,ab.
80	(financ* or fee or fees or expenditure* or saving*).ti,ab.
81	(value adj2 (money or monetary)).ti,ab.
82	resourc* allocat*.ti,ab.
83	(fund or funds or funding* or funded).ti,ab.
84	(ration or rations or rationing* or rationed).ti,ab.
85	or/69-84
86	quality adjusted life year/
87	"quality of life index"/
88	short form 12/ or short form 20/ or short form 36/ or short form 8/
89	sickness impact profile/
90	(quality adj2 (wellbeing or well being)).ti,ab.
91	sickness impact profile.ti,ab.
92	disability adjusted life.ti,ab.
93	(qal* or qtime* or qwb* or daly*).ti,ab.
94	(euroqol* or eq5d* or eq 5*).ti,ab.
95	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
96	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
97	(hui or hui1 or hui2 or hui3).ti,ab.
98	(health* year* equivalent* or hye or hyes).ti,ab.

#	Searches
99	discrete choice*.ti,ab.
100	rosser.ti,ab.
101	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
102	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
103	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
104	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
105	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
106	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
107	or/86-106
108	68 and (85 or 107)

1

2 **Database: HTA via CRD**

3 **Date of last search: 18/09/2023**

#	Searches
1	MESH DESCRIPTOR Infertility EXPLODE ALL TREES
2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*)
3	MESH DESCRIPTOR Endometriosis
4	endometrio*
5	MESH DESCRIPTOR Sperm Count
6	MESH DESCRIPTOR Sperm Motility
7	MESH DESCRIPTOR Sperm Transport
8	((mild* or moderat*) near4 (male* next factor*))
9	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or sub-optimal* or deform* or weak* or inadequat* or sub-standard* or substandard*) near2 (sperm* or semen*))
10	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*)
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	MESH DESCRIPTOR Reproductive Techniques, Assisted
13	(((artificial* or assist*) near2 (conception* or reproduct*)) or ART)
14	MESH DESCRIPTOR Ovulation Induction EXPLODE ALL TREES
15	(ovulat* near2 (induc* or stimulat* or control* or time* or timing*))
16	(ovar* near2 (stimulat* or induc* or hyperstimulat*))
17	(superovulat* or (super next ovulat*))
18	(COS or COH)
19	MESH DESCRIPTOR Gonadotropins
20	MESH DESCRIPTOR Follicle Stimulating Hormone EXPLODE ALL TREES
21	(gonadotrophin* or gonadotropi*)
22	(((follicle next stimulating) or folliculostimulating or folliculo-stimulating) near2 hormone*)
23	(FSH or rFSH or recFSH or uFSH or rhFSH or hpFSH or pFSH or follitropin or follitrophin or follitropine or follicotropin or folltropin or fertiline or fertinom or fertiline or anthrogon or puregon or metrodin or afolia or bemfola or da-3801 or da3801 or fe-999049 or fe999049 or fertavid or folitime or follistim or fostirel or gonadopin or gonal-f or lm-00 or lm001 or org-32489 or org32489 or ovaleap or primapur or recagon or rekovelle or sj-0021 or sj0021 or xm-17 or xm17 or corifollitropin or elonva)
24	MESH DESCRIPTOR Menotropins EXPLODE ALL TREES
25	(HMG or hMGhp or menotrop* or "61489-71-2" or "8049-76-1" or "97048-13-0" or cp-89044 or cp89044 or cp-90033 or cp90033 or humegon or humergon or menogon or menopur or normegon or org-31338 or org31338 or pergonal or neopergonal or homogonal or gonadoryl or meriofert or merional or normegon or preg-norm or pregova or repronex)
26	(urofollitrop* or metrodine or metrodin or fostimon or follitrin or follimon or follegon or fertinorm or fertinex or bravelle or altermon)
27	MESH DESCRIPTOR Selective Estrogen Receptor Modulators
28	MESH DESCRIPTOR Clomiphene

#	Searches
29	MESH DESCRIPTOR Raloxifene Hydrochloride
30	MESH DESCRIPTOR Tamoxifen
31	(anti-oestrogen* or anti-estrogen* or antioestrogen* or antiestrogen*)
32	(SERMs or SERM)
33	((oestrogen* or estrogen* or estradiol or oestradiol) near3 (modulator* or inhibitor* or antagonist* or blocker* or suppress*))
34	(tamoxifen or fulvestrant or faslodex or toremifene or fareston or nolvadex or novaldex or soltamox or tomaxithen or zitazonium or clomifene or clomid or androxal or clomiphene or clomiphen or chloramiphene or clomide or clomifen or clostilbegit or clostilbegyt or enclomid or enclomifene or enclomiphen* or serophene or trans-clomiphene or zuclomifene or dyneric or gravosan or klostilbegit or uclomiphene or raloxifene or evista or keoxifene or isomer)
35	MESH DESCRIPTOR Aromatase Inhibitors
36	MESH DESCRIPTOR Letrozole
37	((aromatase near2 (inhibit* or antagonist*)) or letrozole or femara or anastrozole)
38	MESH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES
39	(((artificial* or assist* or intrauter* or intra-uter*) near2 inseminat*) or ICSI or "IC SI" or IUI)
40	(eutelegeneses or eutelegenesis or IUI or AIH)
41	MESH DESCRIPTOR Fertilization in Vitro
42	MESH DESCRIPTOR Sperm Injections, Intracytoplasmic
43	(IVF or ((in next vitro next fertili*) or (invitro next fertili*)))
44	((intracytoplasm* or (intra next cytoplasm*) or microinject* or (micro next inject*) or transfer*) near2 sperm*)
45	MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES
46	((embryo* or blastocyst*) near2 (transfer* or transplant* or transport*))
47	MESH DESCRIPTOR Coitus
48	MESH DESCRIPTOR Watchful Waiting
49	((active* near1 surveill*) or (clinical near1 observ*) or (expect* near2 (approach* or manag*)) or (no next intervention*) or (no next therap*) or (no next treatment*) or (without near1 (intervention* or therap* or treatment*)) or (wait* near1 see*) or (watch* near2 wait*))
50	((coital or coitus or intercourse* or sex*) near1 (frequen* or regular* or unprotect* or tim*))
51	(((artificial* or modifi* or natural*) near3 cycle*) or NCIVF)
52	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51
53	#11 and #52
54	(#11 and #52) IN HTA FROM 2000 TO 2023

1 Database: INAHTA

2 Date of last search: 18/09/2023

#	Searches
1	"Infertility"[mhe]
2	(steril* or "sub-fertile" or "sub-fertility" or "sub fertile" or "sub fertility" or subfertil* or infertil* or infecund* or "sub-fecund" or "sub-fecundity" or "sub fecund" or "sub fecundity" or subfecund* or hypofertil*)
3	"Endometriosis"[mh]
4	endometrio*
5	"Sperm Count"[mh]
6	"Sperm Motility"[mh]
7	"Sperm Transport"[mh]
8	((mild* or moderat*) AND (male* AND factor*))
9	((abnormal* or block* or defect* or deficien* or fail* or immobil* or immotil* or impair* or insufficien* or low* or reduc* or suboptimal* or "sub-optimal" or "sub-optimally" or "sub optimal" or "sub optimally" or deform* or weak* or inadequat* or "sub-standard" or "sub-standards" or "sub standard" or "sub standards" or substandard*) AND (sperm* or semen*))
10	(asthenospermi* or asthenoteratozoospermi* or asthenozoospermi* or cryptozoospermi* or cryptospermi* or globozoospermi* or hypospermatogen* or oligospermi* or oligozoospermi* or teratospermi* or teratozoospermi*)
11	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
12	Limit to English language, year 2000-2023

Health Economic Quality-of Life Literature Search Strategies

Database: Ovid MEDLINE(R) ALL <1946 to February 06, 2024>

Date of last search: 07/02/2024

#	Searches
1	Fertility/
2	exp Infertility/
3	(fertil* or steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
4	or/1-3
5	limit 4 to english language
6	letter/
7	editorial/
8	news/
9	exp historical article/
10	Anecdotes as topic/
11	comment/
12	case reports/
13	(letter or comment*).ti.
14	or/6-13
15	randomized controlled trial/ or random*.ti,ab.
16	14 not 15
17	animals/ not humans/
18	exp Animals, Laboratory/
19	exp Animal Experimentation/
20	exp Models, Animal/
21	exp Rodentia/
22	(rat or rats or rodent* or mouse or mice).ti.
23	or/16-22
24	5 not 23
25	quality-adjusted life years/
26	sickness impact profile/
27	(quality adj2 (wellbeing or well being)).ti,ab.
28	sickness impact profile.ti,ab.
29	disability adjusted life.ti,ab.
30	(qal* or qtime* or qwb* or daly*).ti,ab.
31	(euroqol* or eq5d* or eq 5*).ti,ab.
32	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34	(hui or hui1 or hui2 or hui3).ti,ab.
35	(health* year* equivalent* or hye or hyes).ti,ab.
36	discrete choice*.ti,ab.
37	rosser.ti,ab.
38	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44	or/25-43
45	24 and 44

1 **Database: Embase <1974 to 2024 February 06>**

2 **Date of last search: 07/02/2024**

#	Searches
1	exp fertility/
2	exp infertility/
3	(fertil* or steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
4	or/1-3
5	limit 4 to english language
6	letter.pt. or letter/
7	note.pt.
8	editorial.pt.
9	case report/ or case study/
10	(letter or comment*).ti.
11	or/6-10
12	randomized controlled trial/ or random*.ti,ab.
13	11 not 12
14	animal/ not human/
15	nonhuman/
16	exp Animal Experiment/
17	exp Experimental Animal/
18	animal model/
19	exp Rodent/
20	(rat or rats or rodent* or mouse or mice).ti.
21	or/13-20
22	5 not 21
23	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
24	22 not 23
25	quality adjusted life year/
26	"quality of life index"/
27	short form 12/ or short form 20/ or short form 36/ or short form 8/
28	sickness impact profile/
29	(quality adj2 (wellbeing or well being)).ti,ab.
30	sickness impact profile.ti,ab.
31	disability adjusted life.ti,ab.
32	(qal* or qtime* or qwb* or daly*).ti,ab.
33	(euroqol* or eq5d* or eq 5*).ti,ab.
34	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
35	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
36	(hui or hui1 or hui2 or hui3).ti,ab.
37	(health* year* equivalent* or hye or hyes).ti,ab.
38	discrete choice*.ti,ab.
39	rosser.ti,ab.
40	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
41	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
42	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
43	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
44	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
45	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
46	or/25-45
47	24 and 46

3 **Database: INAHTA**

1 **Date of last search: 07/02/2024**

#	Searches
1	"Fertility"[mh]
2	"Infertility"[mhe]
3	(fertil* or steril* or "sub-fertile" or "sub-fertility" or subfertil* or infertil* or infecund* or "sub-fecund" or "sub-fecundity" or "sub fecund" or "sub fecundity" or subfecund* or hypofertil*)
4	#3 OR #2 OR #1

2 **Database: HTA via CRD**

3 **Date of last search: 07/02/2024**

#	Searches
1	(MESH DESCRIPTOR Fertility)
2	(MESH DESCRIPTOR Infertility EXPLODE ALL TREES)
3	(fertil* or steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*)
4	#1 OR #2 OR #3
5	(#1 OR #2 OR #3) IN HTA

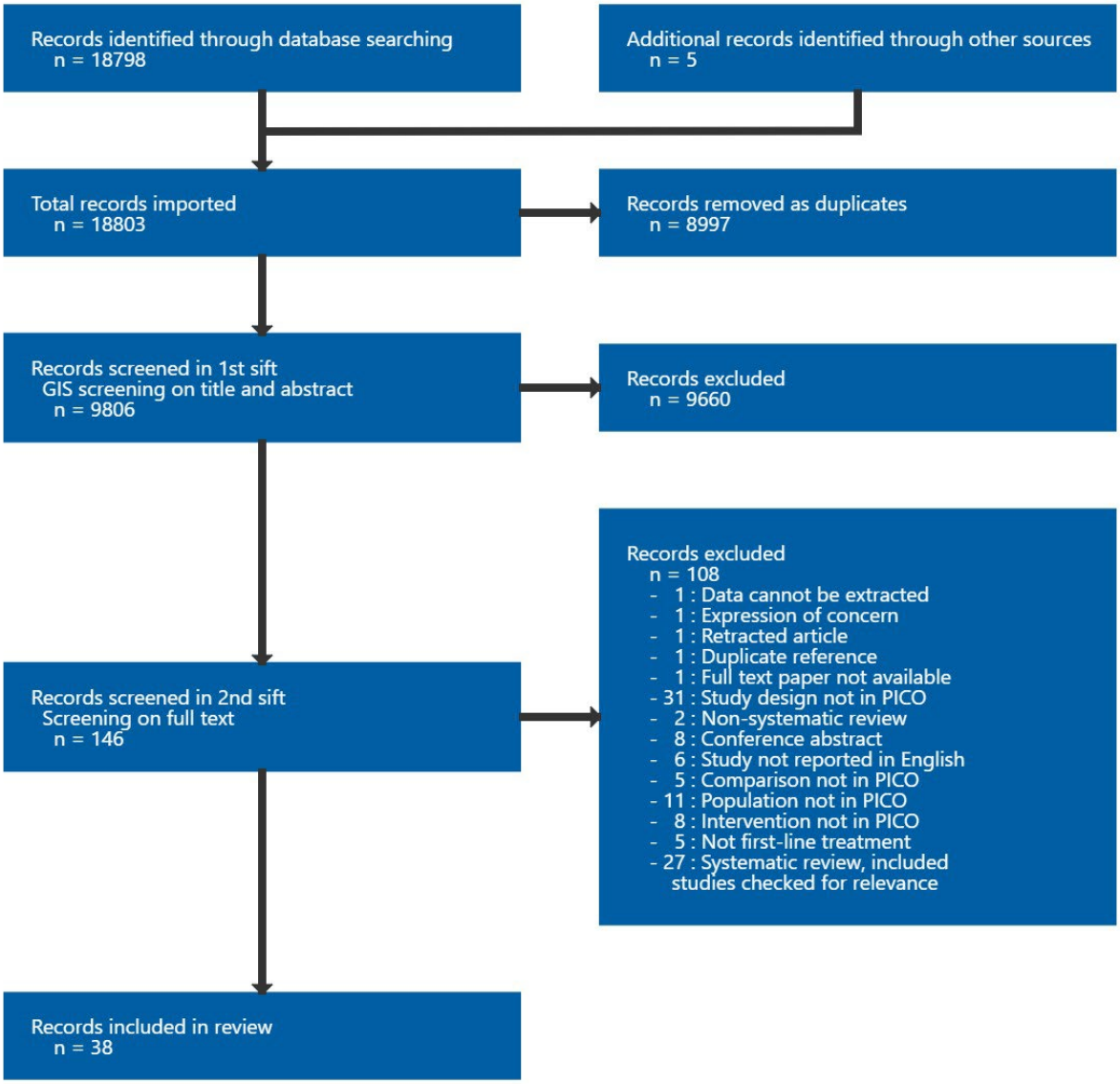
4

Appendix C Effectiveness evidence study selection

Study selection for: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Clinical search

Figure 19: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Please refer to Supplement K Evidence tables for ART

Appendix E Forest plots

Forest plots for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

This section includes forest plots only for outcomes that are meta-analysed in pairwise meta-analyses. Pairwise meta-analysis was only performed for important (but not critical) outcomes. Important outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 20: Clomifene citrate versus expectant management in a mixed prognosis population: Pregnancy loss (denominator: clinical pregnancy)

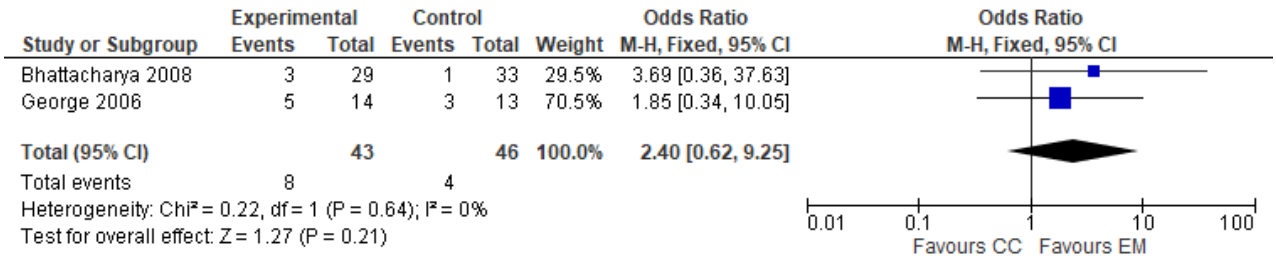


Figure 21: IUI + clomifene citrate versus IUI + letrozole/anastrozole in a mixed prognosis population: Pregnancy loss (denominator: clinical pregnancy)

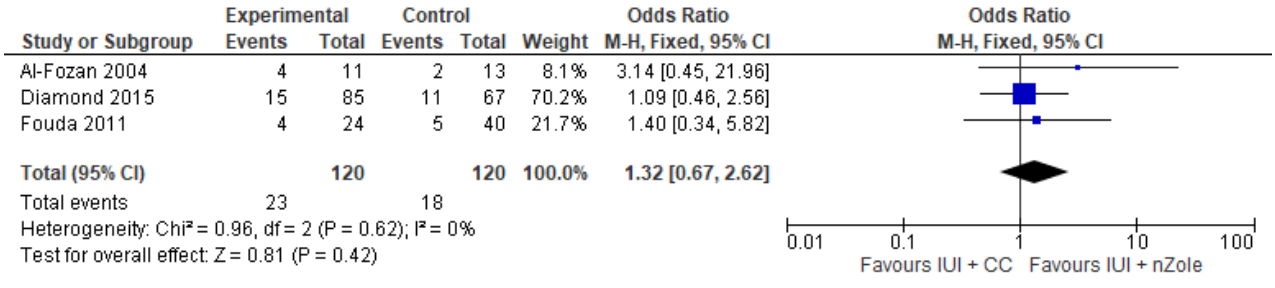


Figure 22: IUI + clomifene citrate versus IUI + letrozole/anastrozole in a mixed prognosis population: Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)

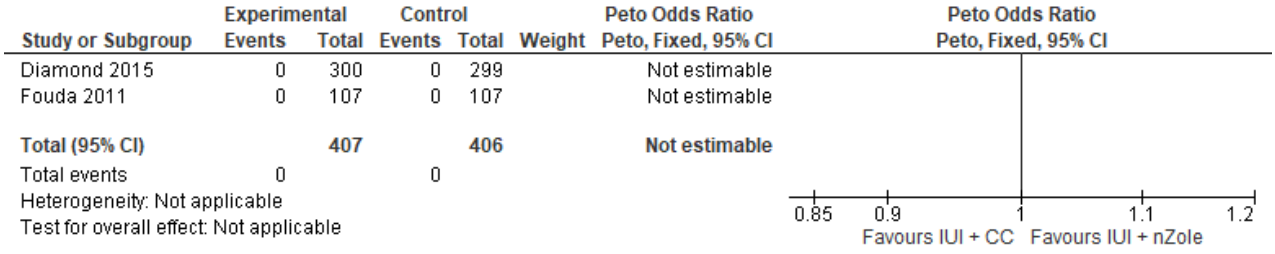


Figure 23: IUI + clomifene citrate versus IUI + gonadotropin in a mixed prognosis population: Pregnancy loss (denominator: clinical pregnancy)

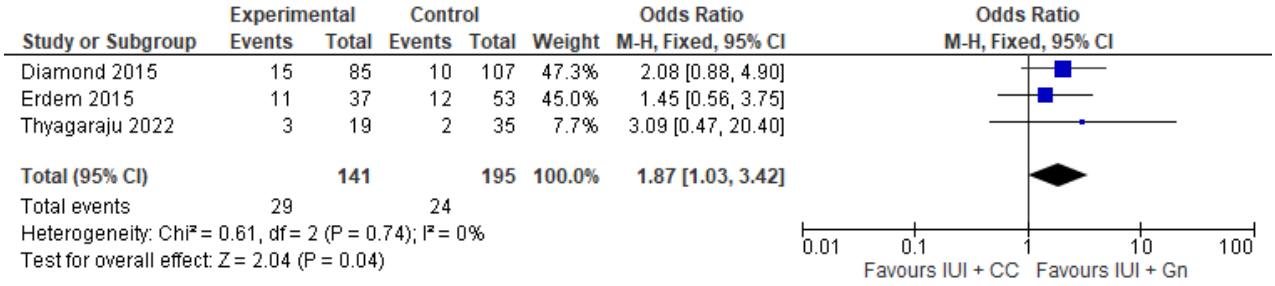


Figure 24: IUI + clomifene citrate versus IUI + gonadotropin in a mixed prognosis population: Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)

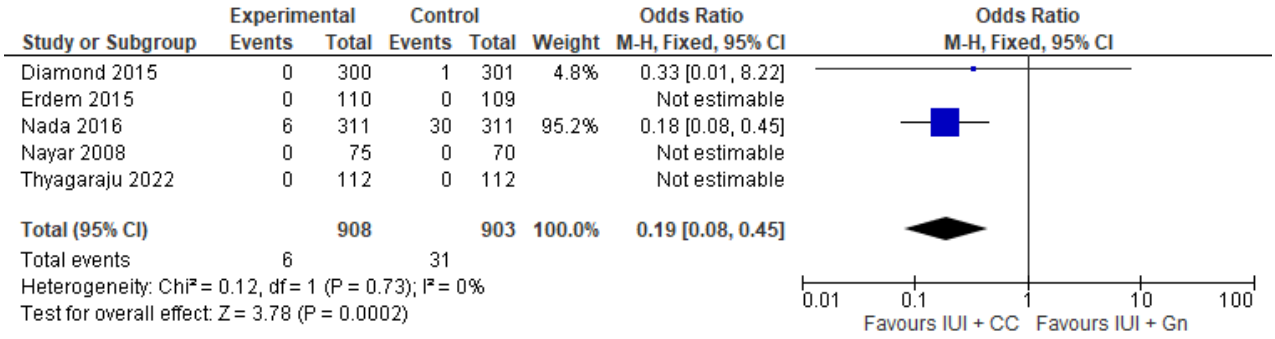


Figure 25: IUI with gonatropin + clomifene citrate versus IUI with gonadotropin + letrozole/anastrozole in a mixed prognosis population: Pregnancy loss (denomnator: clinical pregnancy)

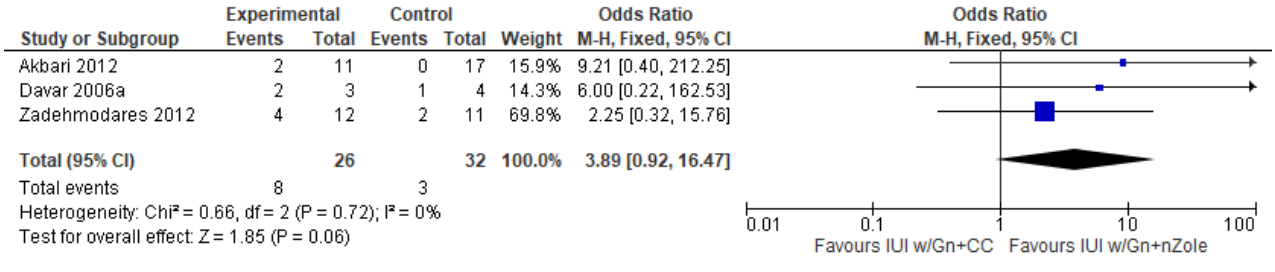


Figure 26: IUI with gonatropin + clomifene citrate versus IUI with gonadotropin + letrozole/anastrozole in a mixed prognosis population: Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)

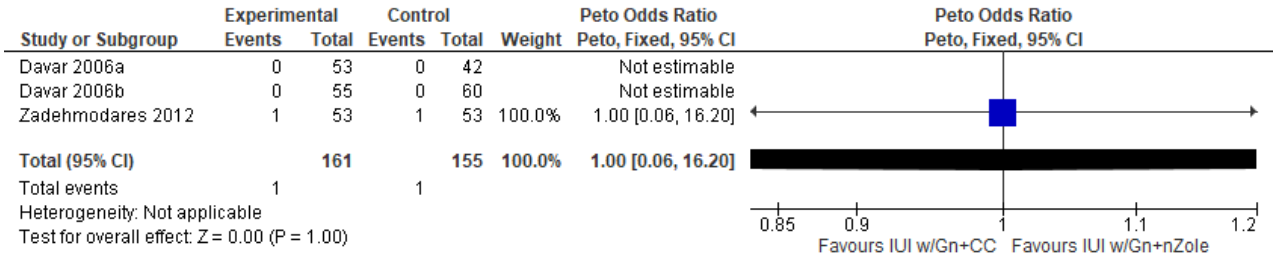
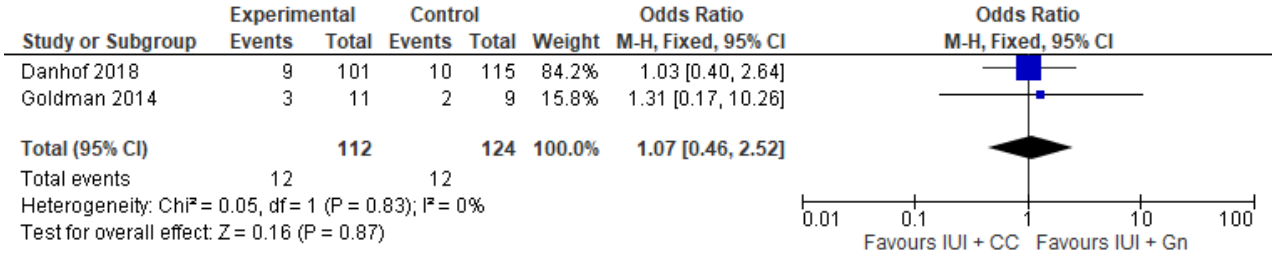


Figure 27: IUI + clomifene citrate versus IUI + gonadotropin in a poor prognosis population: Pregnancy loss (denominator: clinical pregnancy)



Appendix F GRADE tables

GRADE tables for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Table 22: Evidence profile for clomifene citrate versus expectant management in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clomifene citrate	Expectant management	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/43 (18.6%)	4/46 (8.7%)	OR 2.4 (0.62 to 9.25)	99 more per 1000 (from 31 fewer to 381 more)	VERY LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; OR: odds ratio
**See corresponding forest plot*
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 23: Evidence profile for clomifene citrate versus IUI (without ovarian stimulation) in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clomifene citrate	IUI (without OS)	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Bhattacharya 2008)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/29 (10.3%)	0/43 (0%)	OR 11.49 (0.57 to 231.32)	10 more per 1000 (from 20 fewer to 220 more)[3]	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio; OS: ovarian stimulation
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs
[3] Absolute effect calculated based on risk difference

Table 24: Evidence profile for clomifene citrate versus letrozole/anastrozole in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clomifene citrate	Letrozole/ anastrozole	Relative (95% CI)	Absolute		
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
1 (Ibrahim 2012)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/134 (0%)	0/136 (0%)	not estimable	not estimable	LOW	IMPORTANT

CI: confidence interval
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 25: Evidence profile for IUI (without ovarian stimulation) versus expectant management in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI (without OS)	Expectant management	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Bhattacharya 2008)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/43 (0%)	1/33 (3%)	OR 0.25 (0.01 to 6.31)	23 fewer per 1000 (from 30 fewer to 134 more)	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio; OS: ovarian stimulation
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 26: Evidence profile for IUI + clomifene citrate versus IUI + letrozole/anastrozole in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI + clomifene citrate	IUI + letrozole/ anastrozole	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
3*	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	23/120 (19.2%)	18/120 (15%)	OR 1.32 (0.67 to 2.62)	39 more per 1000 (from 44 fewer to 166 more)	LOW	IMPORTANT
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
2*	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/407 (0%)	0/406 (0%)	not estimable	not estimable	HIGH	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio
**See corresponding forest plot*
[1] 95% CI crosses 2 MIDs

Table 27: Evidence profile for IUI + clomifene citrate versus IUI + gonadotropin in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI + clomifene citrate	IUI + gonadotropin	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
3*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/141 (20.6%)	24/195 (12.3%)	OR 1.87 (1.03 to 3.42)	85 more per 1000 (from 3 more to 201 more)	LOW	IMPORTANT
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
5*	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/908 (0.66%)	31/903 (3.4%)	OR 0.19 (0.08 to 0.45)	28 fewer per 1000 (from 19 fewer to 31 fewer)	LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio
**See corresponding forest plot*
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID
[3] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 28: Evidence profile for IUI + letrozole/anastrozole versus IUI (without ovarian stimulation) in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI + letrozole/ anastrozole	IUI (without OS)	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Huang 2021)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/14 (21.4%)	3/13 (23.1%)	OR 0.91 (0.15 to 5.58)	16 fewer per 1000 (from 188 fewer to 395 more)	LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio; OS: ovarian stimulation
[1] 95% CI crosses 2 MIDs

Table 29: Evidence profile for IUI + letrozole/anastrozole versus IUI + gonadotropin in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI + letrozole/ anastrozole	IUI + gonadotropin	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Diamond 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/67 (16.4%)	10/107 (9.3%)	OR 1.91 (0.76 to 4.77)	71 more per 1000 (from 21 fewer to 236 more)	LOW	IMPORTANT
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
1 (Diamond 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/299 (0%)	1/301 (0.33%)	POR 0.14 (0 to 6.87)	3 fewer per 1000 (from 3 fewer to 20 more)	LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; POR: peto odds ratio; OR: odds ratio
[1] 95% CI crosses 2 MIDs

Table 30: Evidence profile for IUI with gonatropin + clomifene citrate versus IUI with gonadotropin + letrozole/anastrozole in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI with gonadoropin + clomifene citrate	IUI with gonadotropin + letrozole/ anastrozole	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
3*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/26 (30.8%)	3/32 (9.4%)	OR 3.89 (0.92 to 16.47)	193 more per 1000 (from 7 fewer to 536 more)	VERY LOW	IMPORTANT
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
3*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/161 (0.62%)	1/155 (0.65%)	POR 1 (0.06 to 16.2)	0 fewer per 1000 (from 6 fewer to 98 more)	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; POR: peto odds ratio; OR: odds ratio
**See corresponding forest plot*
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID
[3] 95% CI crosses 2 MIDs

Table 31: Evidence profile for IVF versus IUI + gonadotropin in a mixed prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVF	IUI + gonadotropin	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Elzeiny 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/6 (16.7%)	2/4 (50%)	OR 0.2 (0.01 to 3.66)	333 fewer per 1000 (from 490 fewer to 285 more)	VERY LOW	IMPORTANT

Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
1 (Elzeiny 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/11 (0%)	0/33 (0%)	Not estimable	Not estimable	LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; IVF: in vitro fertilisation; MID: minimally important difference; OR: odds ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 32: Evidence profile for IUI + clomifene citrate versus expectant management in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IUI + clomifene citrate**	**Expectant management**	**Relative (95% CI)**	**Absolute**		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Farquhar 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/37 (27%)	2/11 (18.2%)	OR 1.67 (0.31 to 9.08)	89 more per 1000 (from 117 fewer to 487 more)	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 33: Evidence profile for IUI + clomifene citrate versus IUI + gonadotropin in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IUI + clomifene citrate**	**IUI + gonadotropin**	**Relative (95% CI)**	**Absolute**		
Pregnancy loss (denominator: clinical pregnancy)												
2*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/112 (10.7%)	12/124 (9.7%)	OR 1.07 (0.46 to 2.52)	6 more per 1000 (from 50 fewer to 116 more)	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio
**See corresponding forest plot*
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 34: Evidence profile for IUI + gonadotropin versus expectant management in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IUI + gonadotropin	Expectant management	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Steures 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/42 (31%)	6/40 (15%)	OR 2.54 (0.86 to 7.53)	160 more per 1000 (from 18 fewer to 421 more)	LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; MID: minimally important difference; OR: odds ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID

Table 35: Evidence profile for IVF versus IUI + clomifene citrate in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVF	IUI + clomifene citrate	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Goldman 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/25 (36%)	3/11 (27.3%)	OR 1.5 (0.32 to 7.12)	87 more per 1000 (from 166 fewer to 455 more)	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; IVF: in vitro fertilisation; MID: minimally important difference; OR: odds ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 36: Evidence profile for IVF versus IUI + gonadotropin in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVF	IUI + gonadotropin	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Goldman 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/25 (36%)	2/9 (22.2%)	OR 1.97 (0.34 to 11.57)	138 more per 1000 (from 134 fewer to 546 more)	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; IVF: in vitro fertilisation; MID: minimally important difference; OR: odds ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 37: Evidence profile for IVF versus IUI + clomifene citrate/gonadotropin in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVF	IUI + clomifene citrate/ gonadotropin	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Bensdorp 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/135 (12.6%)	16/132 (12.1%)	OR 1.04 (0.5 to 2.17)	4 more per 1000 (from 57 fewer to 109 more)	VERY LOW	IMPORTANT
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
1 (Bensdorp 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/201 (1%)	1/207 (0.48%)	POR 2.01 (0.21 to 19.47)	5 more per 1000 (from 4 fewer to 89 more)	VERY LOW	IMPORTANT

CI: confidence interval; IUI: intrauterine insemination; IVF: in vitro fertilisation; MID: minimally important difference; POR: peto odds ratio; OR: odds ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Table 38: Evidence profile for IVF versus IVF modified natural cycle in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVF	IVF modified natural cycle	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Bensdorp 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/135 (12.6%)	16/115 (13.9%)	OR 0.89 (0.43 to 1.86)	13 fewer per 1000 (from 74 fewer to 92 more)	VERY LOW	IMPORTANT
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
1 (Bensdorp 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/201 (1%)	0/194 (0%)	POR 7.17 (0.45 to 115.12)	10 more per 1000 (from 10 fewer to 30 more)[3]	VERY LOW	IMPORTANT

CI: confidence interval; IVF: in vitro fertilisation; MID: minimally important difference; POR: peto odds ratio; OR: odds ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs
[3] Absolute effect calculated based on risk difference

Table 39: Evidence profile for IVF modified natural cycle versus IUI + clomifene citrate/gonadotropin in a poor prognosis population

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVF modified natural cycle	IUI + clomifene citrate/ gonadotropin	Relative (95% CI)	Absolute		
Pregnancy loss (denominator: clinical pregnancy)												
1 (Bensdorp 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/115 (13.9%)	16/132 (12.1%)	OR 1.17 (0.56 to 2.46)	18 more per 1000 (from 50 fewer to 132 more)	VERY LOW	IMPORTANT
Ovarian hyperstimulation syndrome (OHSS; denominator: N randomised)												
1 (Bensdorp 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/194 (0%)	1/207 (0.48%)	POR 0.14 (0 to 7.28)	4 fewer per 1000 (from 5 fewer to 30 more)	VERY LOW	IMPORTANT

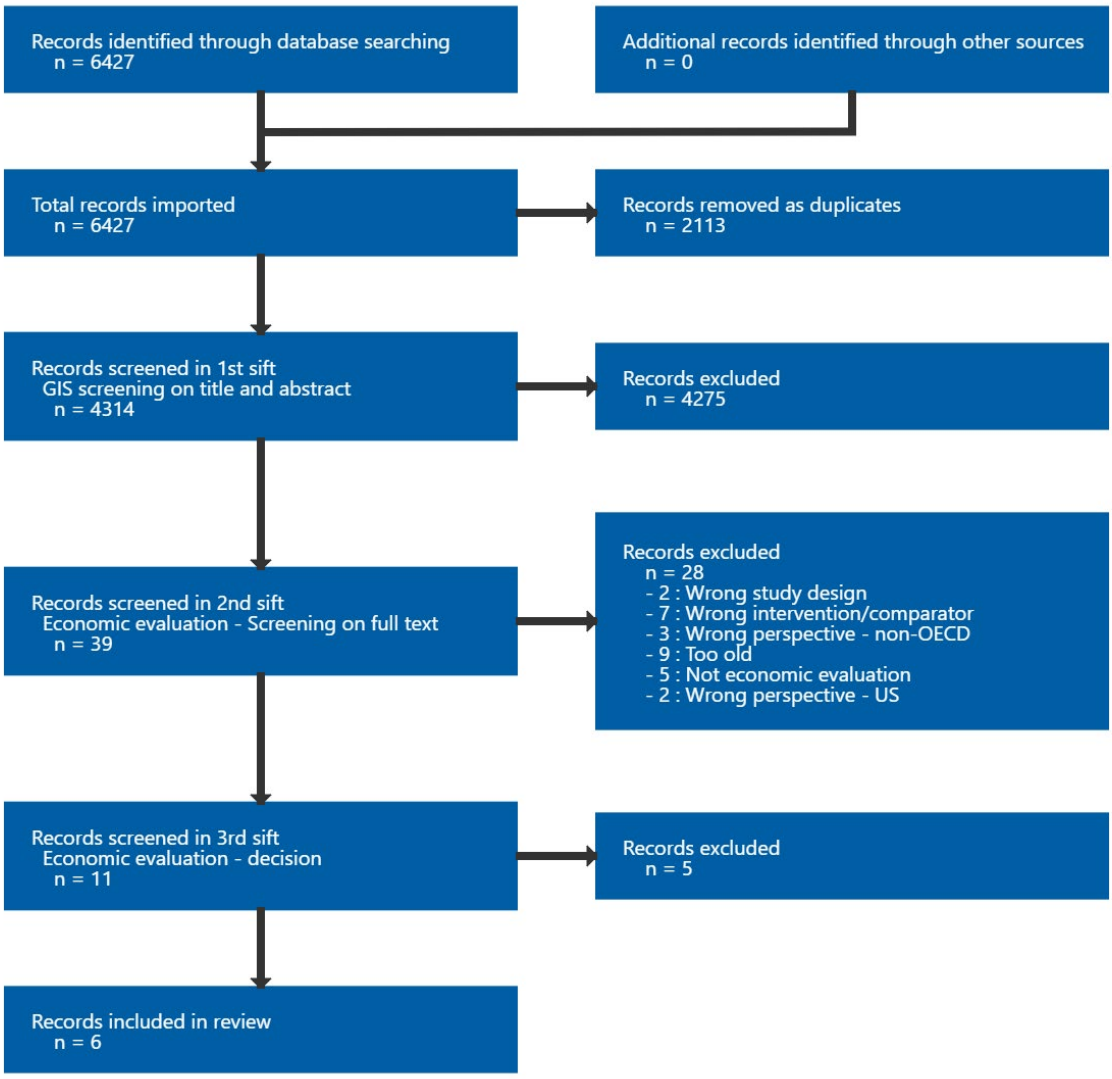
CI: confidence interval; IUI: intrauterine insemination; IVF: in vitro fertilisation; MID: minimally important difference; POR: peto odds ratio; OR: odds ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Six health economic studies were included for this review question.

Figure 28: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Table 40: Economic evidence tables for unexplained subfertility

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: van Eeleken 2020 **Country:** Netherlands **Type of economic analysis:** CEA **Source of funding:** Work supported by a grant from the Dutch Organisation for Health Research and Development (ZonMw)	**1.** IVF-EM-EM (immediate IVF) **2.** EM-IVF-EM (delayed IVF) **3.** EM-EM-IVF (postponed IVF – initial period of EM. If EM is unsuccessful, EM is conducted again. If no live birth after this IVF is provided)	**Population characteristics:** Couples with unexplained subfertility who present at a fertility clinic and where the woman is 38 years old or younger **Modelling approach:** Decision analytic model **Source of baseline data:** Wang 2019 (NMA) **Source of effectiveness data**: • van Eekelen 2017	**Costs:** Societal perspective (healthcare perspective also reported as part of SA) *Societal perspective costs include work absence associated with interventions (IUI-OS & IVF)* **Mean cost per participant:** • IVF-EM-EM – €6,798 • EM-IVF-EM – €4,851	**ICERs:** Intervention **1** dominated by intervention**3** Intervention **2** dominated by intervention **3** Intervention **3 – *reference case (0)*** Intervention **4** dominated by intervention **5** ICER for intervention **5**: €31,141 *Dominated = more costly and less effective* **Probability of being cost effective:**	**Currency:** Euros (€) **Cost year:** 2018 **Time horizon:** Three years **Discounting:** Costs: 4% Health outcomes: 1.5% **Applicability:** Partially applicable **Limitations:** Potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	4. IUIOS-IVF-EM (immediate IUI) **5.** EM-IUIOS-IVF (delayed IUI)	• Custers 2007 • Dutch annual IVF reports • Arce 2005 • Braakhekke 2014 **Source of cost data**: Unit costs for interventions applied to each health state / intervention **Source of unit cost data:** Dutch medical centre cost data	• EM-EM-IVF – €3,999 • IUIOS-IVF-EM – €8,976 • EM-IUIOS-IVF – €6,637 **Primary measure of outcome**: Cost per live birth **Mean outcome per participant:** Not reported	EM-EM-IVF (3) has the probability of having the highest NMB – i.e. being the most cost-effective **Subgroup analysis**: Probability of live birth – 10%, 20%, 30% or 40% over the first year (representing increased age at 10% vs younger age at 40%) *All four analyses showed the same dominance pattern as the primary analysis, with EM-EM-IVF and EM-IUIOS-IVF being the remaining policies to compare.* *The ICERs for EM-IUIOS-IVF compared to EM-EM-IVF for the four prognoses groups were: €59,000 €36,000 €30,000 €28,000, respectively (10% – 40% with increments of 10%)* *EM-EM-IVF was the most likely to yield the highest benefit up to €60,000 (10% prognosis) decreasing to €29,000 (40% prognosis), after which EM-IUIOS-IVF was the most likely to yield the highest net benefit.* **Sensitivity analysis:**	**Other comments:** Probabilistic sensitivity analysis undertaken **<u>Results when indirect costs removed:</u>** ICER for intervention 5: €9,443 Mean cost per participant: • IVF-EM-EM – €2,923 • EM-IVF-EM – €2,091 • EM-EM-IVF – €1,729 • IUIOS-IVF-EM – €3,403 • EM-IUIOS-IVF – €2,529

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				Time horizon of 1.5 years – each period comprising 6 months *Same dominance pattern as in the primary analysis was found. The ICER of EM-IUIOS-IVF compared to EM-EM-IVF was €18,000.* Indirect costs removed *Average costs were considerably lower compared to the primary analysis – ICERs also lower.* *The same dominance pattern as in the primary analysis was found. The ICER of EM-IUIOS-IVF compared to EM-EM-IVF was €9,400* *See other comments for cost breakdown* Fixed odds ratio for IVF over time, instead of increasing the odds ratio by 1 a year *EM-IUIOS-IVF was now dominated by IVF-EM-EM, yielding a higher cumulative probability of live birth at a lower cost.*	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				Up to a value of €44,000 per live birth, EM-EM-IVF was the most likely to yield the highest net benefit, after which none of the other policies reached a probability over 50% to yield the highest net benefit. Probability distributions used for the probability of multiple pregnancy instead of assuming fixed values of 1% for EM, 6% for IUI-OS and 3.3% for IVF *Negligible influence on the results*	
Author and year: Tjon-Kon-Fat 2015 **Country:** Netherlands **Type of economic analysis:** CEA **Source of funding:** Supported by a grant from the Dutch Organisation for Health Research and Development (ZonMw)	IVF single embryo transfer (IVF-SET): n=201 IVF with mildly stimulated or modified natural cycle (IVF-MNC): n=194 IUI with controlled ovarian hyperstimulation (IUI-COH): n=207 *In the base case analysis ovarian hyperstimulation*	**Population characteristics:** Couples with unexplained or mild male subfertility, with a female partner between 18 and 38 years **Modelling approach:** Within-trial economic analysis	**Costs:** Healthcare perspective **Mean cost per participant:** IVF-SET: €7,187 IVF-MNC: €8,206 IVF-COH: €5,070 **Primary measure of outcome**: Live birth of one healthy child **Mean outcome per participant:** IVF-SET: 0.52	**ICERs:** €43,375 for the delivery of an additional healthy child for IVF-SET compared with IUI-COH IVF-MNC more costly and less effective than both IVF-SET and IVF-COH **Probability of being cost effective:** WTP €60 000 for an additional healthy child – 62% chance that IVF-SET is cost-effective. WTP €135 000 for an additional healthy child – 81% chance that IVF-SET is cost-effective	**Currency:** Euros (€) **Cost year:** 2013 **Time horizon:** 12 months **Discounting:** NA **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	(COH) was conducted with either clomiphene citrate (CC) or follicle stimulating hormone (FSH) according to the local protocol of the participating hospital in the RCT.	**Source of baseline data:** Bensdrop 2015 **Source of effectiveness data**: Bensdrop 2015 **Source of cost data:** Bensdrop 2015 **Source of unit cost data:** • Dutch Formulary on medication • Lukassen 2004 • Academic hospital in the Netherlands	IVF-MNC: 0.43 IUI-COH: 0.47	**Subgroup analysis**: Ongoing pregnancy as effectiveness outcome: €78,098 Live birth rate as effectiveness outcome: €79,365 **Sensitivity analysis:** 15% multiple pregnancy rate in the IUI-COH group (compared to 7%): €13,633 Ongoing pregnancy rate for IVF-SET 75% (instead of 60%): €12,091 UK costs obtained from the website of an NHS teaching hospital: £80,429 When only CC is provided for IUI-COH: *ICER for IUI-COH with only CC: €60,223* When only FSH is provided for IUI-COH: *ICER for IUI-COH with only FSH: €32,322*	Bootstrapping analysis Fertility services are publicly financed through a mandatory insurance package
Author and year: Danhof 2020	**Intervention:** Gonadotrophins	**Population characteristics:** Couples with	**Costs:** Healthcare perspective	**ICERs:** €21,804 per ongoing pregnancy	**Currency:** Euros (€)

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Country: Netherlands **Type of economic analysis:** CEA **Source of funding:** Initial RCT received funding from the Dutch Organisation for Health Research and Development (ZonMw)	**Comparator:** Clomiphene citrate	unexplained subfertility **Modelling approach:** Within-trial economic analysis **Source of baseline data:** Danhof 2018 **Source of effectiveness data**: Danhof 2018 **Source of cost data:** Danhof 2018 **Source of unit cost data:** • Dutch Formulary on Medication • Dutch Consortium • Lukassen 2004	**Mean cost per participant:** Gonadotrophins: €1675 Clomiphene citrate: €1078 **Primary measure of outcome**: Cost per ongoing pregnancy **Mean outcome per participant:** Gonadotrophins: 0.31 Clomiphene citrate: 0.26	**Probability of being cost effective:** NR **Subgroup analysis**: NA **Sensitivity analysis:** Per protocol analysis: *€22,782 per ongoing pregnancy* Cost per additional live birth as effectiveness outcome: *€17,044 per additional live birth* Dosage of 150 IU gonadotrophins (increased dose compared to base case): *€42,432 per ongoing pregnancy*	**Cost year:** 2017 **Time horizon:** 6 months (or until an ongoing pregnancy occurred) **Discounting:** NA **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:** Parametric bootstrapping used to assess uncertainty
Author and year: Wordsworth 2011 **Country:** Scotland	**Intervention:** Clomifene citrate (CC) Intrauterine	**Population characteristics:** Couples with infertility for over 2 years. Confirmed ovulation, patent	**Costs:** Healthcare perspective **Mean cost per participant:**	**ICERs:** CC: Dominated (more costly and less effective compared to EM)	**Currency:** Pounds (£) **Cost year:** 2006

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Type of economic analysis: CEA **Source of funding:** Office of the Scottish Executive Health Department (UK)	Insemination (IUI) **Comparator:** Expectant management (EM)	fallopian tubes and motile sperm **Modelling approach:** Post trial economic analysis **Source of baseline data:** SUIT trial (Bhattachary, 2008) **Source of effectiveness data**: SUIT trial (Bhattachary, 2008) **Source of cost data:** SUIT trial (Bhattachary, 2008) **Source of unit cost data:** SUIT trial (Bhattachary, 2008 – using 2006 prices) and national sources	CC: £349.96 IUI: £331.27 EM: £11.88 **Primary measure of outcome**: Cost per live birth **Mean outcome per participant:** CC: 0.13 IUI: 0.22 EM: 0.17	£5,604 per live birth for IUI compared to EM **Probability of being cost effective:** If the cost–effectiveness ceiling ratio is £30,000: EM has a ~15% chance of being the most cost-effective intervention, while IUI has an ~80% chance At £10,000 for an additional live birth IUI is cost-effective with a probability of ~70% At £4,000 for an additional live birth IUI is cost-effective with a probability of ~30%. **Subgroup analysis**: **Sensitivity analysis:** CC drug costs (50% increase and 50% decrease) • *CC still the dominant strategy for both an increase and decrease in costs* Zero overheads and a 100% increase in overheads, staff costs increase by 50% and the discount rate for capital items at 3.5% instead of 6%.	**Time horizon:** 6 months **Discounting:** NA **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:** Parametric bootstrapping used to assess uncertainty

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				• *The ICER for IUI versus EM treatment was highest when staff costs for IUI were increased by 50% at £6,618 cost per live birth. When overheads were reduced to zero, the ICER was £5,037. Different discount rates had little effect.* Threshold analysis to consider how variations in the live birth rate for CC and IUI would affect results. • *Live birth rate of 27% for IUI resulted in an ICER of £3,082 between IUI and EM, with CC remaining dominated.* • *Live birth rate of 27% for CC. The ICER for IUI and EM remained the same, but the ICER fell when CC was considered indicating that the appropriate comparison in this scenario was CC and EM – with IUI ruled out due to extended dominance. The ICER for CC and EM in this scenario was £3,148.*	
Author and year: van Eekelen 2021 **Country:** Netherlands	**Intervention:** Letrozole + IUI Gonadotrophins + IUI	**Population characteristics:** Couples with unexplained subfertility	**Costs:** Societal / healthcare perspective	**ICERs:** Letrozole: €2,809 Gonadotrophins: €53,831	**Currency:** Euros (€) **Cost year:** 2019

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Type of economic analysis: CEA **Source of funding:** The Dutch Organisation for Health Research and Development (ZonMw)	**Comparator:** Clomifene citrate (CC) + IUI	**Modelling approach:** Decision analytic model **Source of baseline data:** Wang 2020 (NMA) **Source of effectiveness data**: Wang 2020 (NMA) **Source of cost data:** Wang 2020 (NMA) **Source of unit cost data:** Dutch formulary for medication	*Treatments are identical in everything except for stimulation agent, therefore the societal perspective coincides with the healthcare perspective* **Mean cost per participant:** Letrozole: €434 Gonadotrophins: €1,809 CC: €362 **Primary measure of outcome**: Cost per live birth **Mean outcome per participant:** NR <u>Cumulative live birth rate over four cycles:</u> Letrozole: 32.0% Gonadotrophins: 34.5%	**Probability of being cost effective:** Between €1 and €3,000 per live birth, CC has the highest probability of being cost effective (maximally 65% at €1) Between €3,000 and €55,000, Letrozole had the highest probability (maximally 62%) Over, €55,000 or more, gonadotrophins had the highest probability of being cost effective (maximally 56%) **Subgroup analysis**: NA **Sensitivity analysis:** RR for live birth rate after gonadotrophins derived from pooled evidence on all RCTs instead of only RCTs with up to four cycles of IUI: *Letrozole: €2,787* *Gonadotrophins: €19,448* 2 IUI cycles: *Letrozole: €2,208* *Gonadotrophins: €44,746* 6 IUI cycles: *Letrozole: €3,332* *Gonadotrophins: €67,376*	**Time horizon:** Four cycles of IUI (to be completed within a year) **Discounting:** NA **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:** Probabilistic sensitivity analysis undertaken. Costs for procedures regarding IUI treatment were considered identical for all three agents.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Clomifene citrate (CC): 29.4%	Baseline cumulative live birth rate for CC obtained from the total follow up in RCTs: *Letrozole: €2,717* *Gonadotrophins: €56,773* Parameters chosen based on a previous analysis of IPD data: *Letrozole: Dominated by CC* *Gonadotrophins: €20,506*	
Author and year: Bordewijk 2019 **Country:** Netherlands **Type of economic analysis:** CEA **Source of funding:** The Dutch Organisation for Health Research and Development (ZonMw)	**Intervention and comparator:** Four different treatment combinations were evaluated to compare the following: • Gonadotrophins versus Clomifene citrate • And IUI versus intercourse *List of treatments:* Gonadotrophins + IUI **(1)** Gonadotrophins alone **(2)**	**Population characteristics:** Sub fertile women of at least 18 years of age with normogonadrotropic anovulation who had been ovulatory for six cycles on CC, but not conceived **Modelling approach:** Within-trial economic analysis **Source of baseline data:** Weiss 2018	**Costs:** Healthcare perspective **Mean cost per participant:** For each individual intervention: • Gonadotrophins + IUI: €4,984 • Gonadotrophins: €4,003 • CC + IUI: €4,007 • CC: €2,054 **Primary measure of outcome**: Cost per live birth **Mean outcome per participant:**	**ICERs:** Gonadotrophins compared with CC: • €15,258 per additional live birth IUI compared with intercourse: • €24,361 per additional live birth **Probability of being cost effective:** NR **Subgroup analysis**: NA **Sensitivity analysis:** Gonadotrophins compared with CC: • UK costs: £19,744 per live birth • Endpoint ongoing pregnancy: €11,157 per ongoing pregnancy • All CC cycles monitored with ultrasound: €13,460 per live birth	**Currency:** Euros (€) **Cost year:** 2017 **Time horizon:** 8 months **Discounting:** NA **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:** Parametric bootstrapping used to assess uncertainty

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	Clomifene citrate (CC) + IUI **(3)** Clomifene citrate (CC) alone **(4)** The study compared Gonadotrophins to CC by comparing • *1 + 2 to 3 + 4* And compared IUI to intercourse by comparing • *1 + 3 to 2 + 4*	**Source of effectiveness data**: Weiss 2018 **Source of cost data:** Weiss 2018 **Source of unit cost data:** • Average costs from three Dutch hospitals • Lukassen 2004 • One general hospital	For each individual intervention: • Gonadotrophins + IUI: 0.54 • Gonadotrophins: 0.49 • CC + IUI: 0.44 • CC: 0.39	• CC cycles not monitored with ultrasound: €17,222 per live birth <u>IUI compared with intercourse:</u> • UK costs: £34,420 per live birth • Endpoint ongoing pregnancy: €17,531 per ongoing pregnancy	Population is those who have already failed to conceive using CC alone When UK costs were employed in the SA cost were obtained from one UK hospital

Appendix I Economic model

Economic model for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Cost utility analysis of assisted reproduction techniques for people with unexplained health related fertility problems

Introduction

The NICE 2013 guideline (CG156) recommended that intrauterine insemination should not be routinely offered for people with unexplained infertility, mild endometriosis or mild male factor infertility. For this guideline update this decision was revisited with the best available clinical evidence assessed using a network meta-analysis. An original health economic model was developed to evaluate the cost-effectiveness of intrauterine insemination (IUI) as an alternative to IVF as a first line treatment.

Methods

Setting and population

The model setting was for the NHS and the population was people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter. In the base case analysis, it was assumed that treatment was started at 30 years of age, but the impact of alternatives was assessed with sensitivity analysis. A life-time horizon was adopted to value the Quality Adjusted Life Year (QALY) gain from a live birth, although shorter durations were assessed in sensitivity analysis. To estimate cumulative live births a time horizon of remaining female reproductive life was adopted to reflect that expectant management is not time limited and that spontaneous conception can still occur following unsuccessful fertility treatment. However, the impact of shorter assessment periods was considered in sensitivity analyses.

Model structure

Treatment strategies

Clinical effectiveness data for the health economic model was derived from a network meta-analysis (NMA) on live birth rates. A total of 7 treatments were compared in this NMA:

I. Expectant management (EM)
II. Clomifene citrate (CC)
III. IUI without ovarian stimulation (OS)
IV. Clomifene citrate plus IUI
V. Gonadotropins plus IUI
VI. Letrozole or anastrozole plus IUI

VII. IVF fresh or frozen

Clomifene citrate as a standalone fertility treatment performed badly in the network analysis with a point estimate for relative treatment effect worse than expectant management (EM). This was consistent with the previous guideline which had recommended that OS should not be offered to women with unexplained infertility. Therefore, it was concluded that there was little merit in considering this treatment option in the economic analysis.

The committee also agree that expectant management was not in the decision space for this guideline, whilst accepting that spontaneous conception remained possible following unsuccessful treatment. The committee also agreed that IVF should be a second line treatment following unsuccessful IUI and that this would be in line with international practice and guidance (ASRM 2020, Koutsouki 2023), reflecting that IUI is less invasive and less expensive than IVF. However, the committee agreed that IUI as a second line treatment to IVF should not be considered.

Therefore, the following treatment strategies were assessed in this analysis:

1. IVF – EM (IVF | EM)
2. IUI without OS - IVF – EM (IUI without OS | IVF | EM)
3. Clomifene citrate + IUI – IVF – EM (CC + IUI | IVF | EM)
4. Gonadotropins + IUI – IVF – EM (Gn + IUI | IVF | EM)
5. Letrozole/anastrozole + IUI – IVF – EM (nZole + IUI | IVF | EM)

The model was developed so that the following strategies could also be assessed but no results are presented in this report as they were not considered to be in the decision space of strategies that would be recommended:

a) EM
b) Clomifene citrate – EM
c) IUI without OS – EM
d) Clomifene citrate + IUI – EM
e) Gonadotropins + IUI – EM
f) Letrozole/anastrozole + IUI – EM

Treatment cycles

The number of treatment cycles for each intervention, whether utilised as first or second line, was estimated from studies that were included in the network meta-analysis. The assumption made with respect to the maximum number of treatment cycles and the maximum duration of treatment are detailed in Table 41. The maximum duration of treatment is estimated according to assumptions made with respect to treatment spacing. When an intervention is offered as second line, it is assumed that the maximum cycles and maximum treatment duration are the same as would be the case when offered as a first line treatment.

Table 41: Assumptions made for maximum treatment cycles and duration

Treatment	Maximum number of treatment cycles	Maximum treatment duration (months)	Source
IVF	3	6 [a]	Goverde 2000

Treatment	Maximum number of treatment cycles	Maximum treatment duration (months)	Source
IUI with OS	4	8 [b]	Diamond 2015
IUI without OS	6	6 [c]	Bhattacharya 2008

(a) Assumed that there is a 2-month interval between IVF cycles to reflect that it is generally advised that the spacing between fresh IVF cycles should be around 4-6 weeks after a negative pregnancy test which allows for a full menstrual cycle in between.
(b) Guideline committee noted there is no reason for IUI with OS to have a longer spacing than IVF
(c) IUI without OS can proceed in successive menstrual cycles if there is no pregnancy
IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Modelling approach

The model utilised a simple Markov approach as shown in Figure 29 below. The model used a Markov cycle of 1-month to approximate the menstrual cycle. In each cycle women who had not already had a live birth would either remain in a "no birth" health state or transition to the "live birth" state if they had a successful outcome from fertility treatment or a birth from spontaneous conception if treatment was completed. "Live birth" was an absorbing state with any future fertility not considered in the analysis.

The model accounted for the possibility of live birth from expectant management after completion of active treatment for the woman's remaining reproductive life, which was estimated using a published prediction model (van Eekelen 2017).

The decision tree for fertility treatment for the differing model outcomes and events associated with that treatment is illustrated in Figure 30.

Figure 29: Markov schematic to assess fertility treatments across a woman's reproductive life cycle

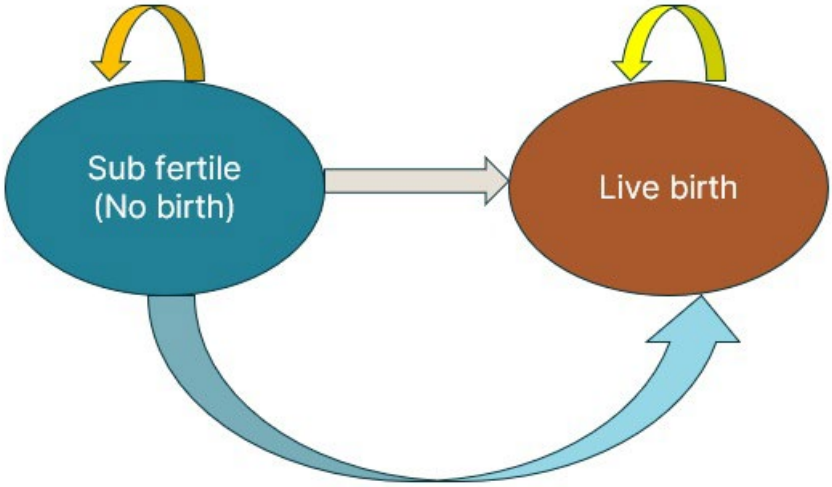
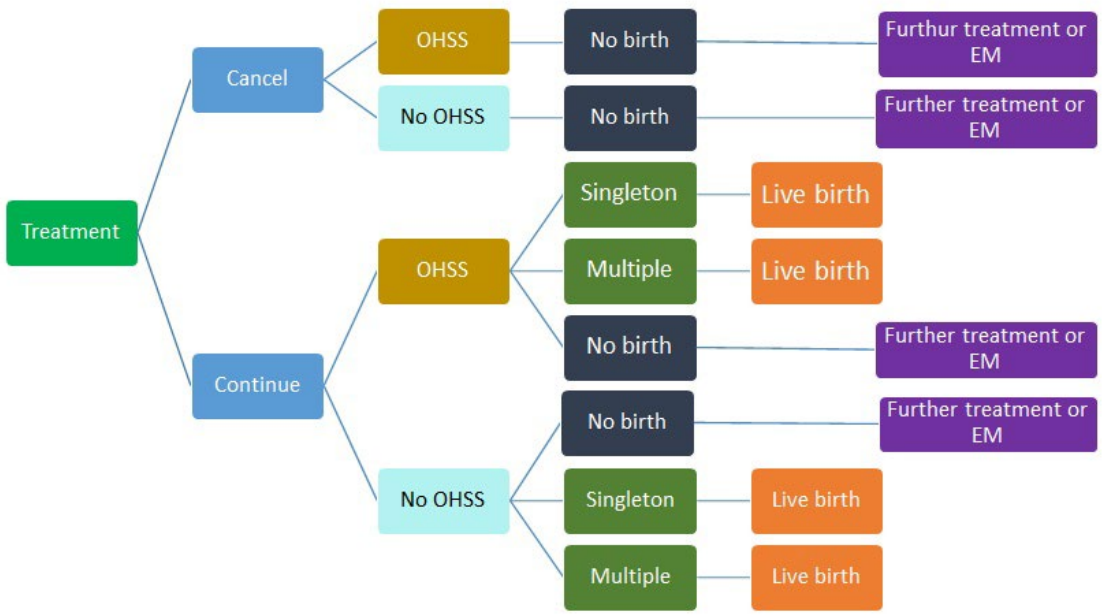


Figure 30: Decision tree illustrating the outcomes of assisted reproduction



EM: expectant management; OHSS: ovarian hyperstimulation syndrome

Clinical outcomes

The clinical outcomes incorporated into the model were:

- Live births
- Singleton/multiple birth
- Ovarian hyperstimulation syndrome (OHSS)

The purpose of fertility treatment is to increase live birth rates compared to those that would be achieved in the absence of treatment, and therefore that is clearly the critical clinical outcome in the model. However, fertility treatment is also associated with higher rates of multiple birth and can lead to OHSS. Multiple pregnancy from IVF is not universally considered an undesirable outcome of fertility treatment (Gleicher, 2009) especially where more than one child is wanted to "complete the family". However, as multiple pregnancy is linked to much higher rates of preterm birth it was included within the model in order to capture its higher costs and to reflect that policy makers have worked to reduce the multiple birth rate from IVF (Our campaign to reduce multiple births | HFEA). OHSS is known as important complication of fertility treatment which can have implications for health-related quality of life and costs.

Baseline

For the base case analysis, cumulative live birth rates for expectant management were estimated from the van Eekelen prediction model for a period of 6 months. Although expectant management is not considered formally as a first line intervention in the economic model, it was utilised as the reference treatment within the NMA. By applying the relative treatment effects to this expectant management baseline, an estimate of the absolute

cumulative live birth rates was obtained for the interventions that are included within the analysis.

A prognostic index (PI) is calculated according to the following formula:

$PI = -1.56 \times -0.37\beta_1 - 0.74\beta_2 - 0.241\beta_3 - 0.359\beta_4 + 0.062\beta_5 - 0.654\beta_6$

Variable names and co-efficient values are outlined in Table 42.

Table 42: Variables and coefficients used in the calculation of the prognostic index

Variable	Coefficient	Coefficient value
Female years below 31 years age [a]	β_1	1
Female years above 31 years age	β_2	0
Duration of subfertility (years)	β_3	2
Primary subfertility	β4	1
Percentage of motile sperm	β_5	40
Referred by a gynaecologist	β_6	1

(a) In the base case analysis, an age of 30 was assumed for the female giving a coefficient value of 31 – 30 = 1
(b) In the base case analysis this was set to zero as female was below 31 years of age
(c) 2 years as this is used within the guideline as a indicator of a medical cause of subfertility
(d) Primary subfertility is a dummy variable and is set to 1 to reflect the population that would be mostly covered by NICE recommendations
(e) We assumed 40% sperm motility to exclude a male factor cause
(f) Referral by a gynaecologist is a dummy variable and is set to 1 to reflect the population that would mostly be covered by NICE recommendations

The PI is then used to estimate the probability of spontaneous conception in the first cycle according to the following formula:

$\mu = e^{(PI)} \div 1 + e^{(PI)}$

In order to estimate the probability of spontaneous conception over a number of cycles the following equation is applied, where m + j represents the number of cycles:

$$\mathbf{1} - \prod_{\boldsymbol{i=m}}^{\boldsymbol{i=m+j-1}} \frac{\mathbf{1} - \boldsymbol{\mu} + \boldsymbol{i} \times \mathbf{0.1}}{\mathbf{1} + \boldsymbol{i} \times \mathbf{0.1}}$$

In probabilistic sensitivity analysis (PSA) this baseline probability was assessed as a deterministic model input.

As an alternative to this prediction model estimate of spontaneous conception, a published study (Bhattacharya, 2008) was used in sensitivity analyses. The parameters for this estimate are shown in Table 43. It was possible to sample this model input in PSA using a beta distribution with the alpha and beta parameters shown.

Table 43: Parameters used to estimate the baseline probability of spontaneous conception with expectant management in sensitivity analysis

Variable	Estimate	Alpha	Beta
Probability of spontaneous conception	13.4%	26	168

Originally, it had been intended to use a network meta-analysis to estimate the baseline risk of multiple birth, however the data was particularly sparse and the limited trial data for multiples with expectant management were much higher than is actually observed and this led to unreliable estimates of relative treatment effect. So instead we used the comprehensive dataset from the Office of National Statistics (ONS, Birth characteristics,

2024) for the year 2021. As this dataset does not distinguish by mode of conception we used data from the HFEA dashboard and published studies to estimate the number of multiples from IVF and IUI conceptions and thereby make an adjustment to the ONS figures in order to derive an estimate of 1.25% for the multiple birth rate from spontaneous conceptions. The data used to inform this estimate is summarised in Table 44 below. For PSA a beta distribution was used to sample the baseline multiple birth rate using alpha and beta values derived from the estimate of events and denominator.

Table 44: Data used to estimate the baseline multiple birth rate

Outcome	Events	Denominator	Source	Notes
Maternities with multiple births in England and Wales	8,470	618,848	ONS 2024	Year 2021
IVF maternities with multiple birth	905	17,795	HFEA	Year 2021
IUI maternities with multiple birth	41	490	Bahadur 2019	Year 2016
Estimated spontaneous maternities with multiple birth	7,524	600,563	Calculated	IVF and IUI events and denominators subtracted from total maternities

Clinical effectiveness and adverse effects

Treatment effectiveness for the live birth outcomes was estimated using the log odds ratios derived from the NMA for interventions relative to expectant management. Simulations of relative treatment effectiveness were undertaken using Bayesian Markov chain Monte Carlo (MCMC) simulation, which sampled directly from the joint posterior distribution from the NMAs, thereby maintaining any correlation between them, in the WinBugs® package. The results output of 120,000 simulations (CODA) was then imported into the Microsoft Excel® model. When running PSA a random number was used to select a row of data (reflecting a single WinBugs® simulation) so that any correlation between the LORs would be preserved. For the deterministic analysis the mean of the log odds ratio from the CODA was used. These values are reproduced in Table 45.

Table 45: Mean log odds ratios for the live birth outcomes for interventions compared to expectant management

Intervention	Log odds ratio
IVF	1.064
IUI without OS	0.386
Clomifene citrate + IUI	0.266
Gonadatropins + IUI	0.820
Letrazole/anastrozole + IUI	0.109

IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

The absolute cumulative probability of live birth over the duration of the intervention was estimated using a logit function as outlined below.

probOUTCOME is the absolute probability for expectant management

Logit = LN (probOUTCOME/(1-probOUTCOME))

Log-odds = Logit + LOR

Absolute probability = EXP(log-odds)/(1+EXP(log-odds))

In the base case analysis, it was assumed that a treatment would be just as effective as a second-line treatment as when utilised first line. However, sensitivity analysis was undertaken to explore to what extent model conclusions might be affected by relaxing this assumption to allow for depletion of susceptibles. This is where people who are more likely to have a successful outcome from an intervention have a better prognosis ('susceptibles'). The remaining (unsuccessful) population have a worse prognosis on average due to the loss/depletion of 'susceptibles' and therefore a second line intervention will not be effective as when the intervention was offered first line.

To take into account the depletion of susceptibles it is assumed that a percentage of the remaining population who did not achieve a live birth with first line treatment have a zero probability of success with either subsequent treatment or expectant management. Effectively, this amounts to assuming that in a population with unexplained fertility there are a proportion who can have a live birth and a proportion who can't (whose unexplained cause effectively means they are infertile rather than sub fertile). In the proportion who can have a live birth the simplifying assumption is made that IVF remains just as effective even if given as a second line intervention.

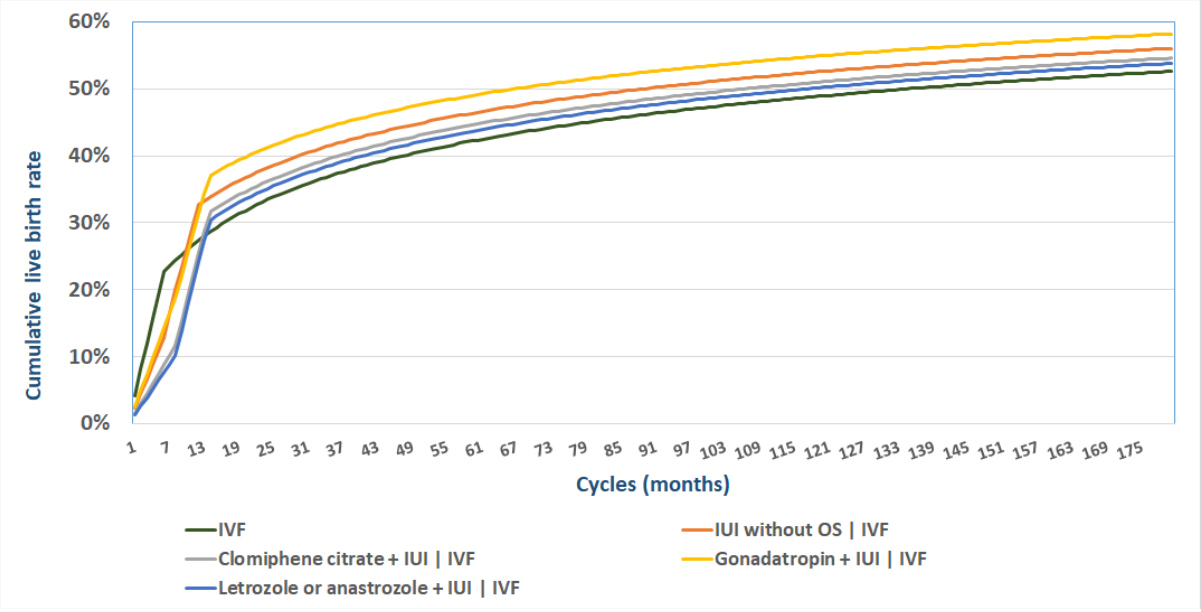
The cumulative live birth probability estimated from the NMA covered a period of several months depending on the number of treatment cycles offered and assumptions about the spacing of treatment cycles. The following formula was used to estimate the cumulative live birth rate per month (Markov cycle) of treatment.

$$1 - (1 - \text{Cumulative live birth rate at end of treatment})^{\wedge(\text{Treatment month} \div \text{Treatment duration in months})}$$

If treatment is completed without a live birth, then it is assumed that birth through spontaneous conception is possible over the remaining time horizon of the model. This is estimated using the van Eekelen prediction model but reflecting an increased duration of subfertility and older age with the passing of time in the model.

Figure 31 shows the cumulative live birth rates for each strategy for the base case analysis.

Figure 31: Cumulative live birth rates for the different intervention strategies in the base case analysis



IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

The relative risk of multiple birth with intervention compared to expectant management was estimated using the events and denominator data in Table 44.

Table 46: Model inputs for the relative risk of multiple birth with intervention compared to expectant management

Intervention	Relative Risk	Lower 95% CI	Upper 95% CI	Distribution[a]
IVF	4.06	3.80	4.34	Log-normal
IUI	6.68	4.98	8.96	Log-normal

(a) For sampling in the probabilistic sensitivity analysis
CI: confidence interval; IUI: intrauterine insemination; IVF: in vitro fertilisation

The risk of OHSS with fertility treatment were estimated using a recently published UK study (Sood, 2022) with the model input parameters based on this paper listed in Table 47. In PSA these risks were sampled using a beta distribution and the alpha and beta parameters shown in the table. It was assumed that mild OHSS was not clinically significant and that it did not have any resource implications. So, the overall OHSS risk relates to OHSS that can be classified as moderate or severe.

Table 47: Model input parameters for OHSS

Outcome	Risk	Alpha	Beta
OHSS overall	0.016	24	1,468
OHSS moderate | OHSS [a]	0.542	13	11
OHSS severe | OHSS [a]	0.458	11	13

(a) The conditional probability given that moderate or severe OHSS has occurred
OHSS: ovarian hyperstimulation syndrome

Costs and resource use

In line with the NICE guidelines manual, a NHS and personnel social services perspective was adopted for this analysis (https://www.nice.org.uk/process/pmg20). Costs were mostly based on a 2022/23 price year. However, NHS Reference Costs were based on the most recently available at the time of writing. In line with the NICE reference case, costs were discounted at a rate of 3.5% per annum.

Unit cost data that was only available from earlier years was updated for inflation to 2022/23 prices using the NHSCII (NHS Cost Inflation Index) and the now discontinued HCHS (Hospital and Community Health Service) index for pre-1917 costs (Unit Costs of Health and Social Care 2023).

Costs were treated as deterministic variables in PSA as the values were not considered to be subject to sampling uncertainty.

Intervention costs are shown in Table 48. In costing IVF treatment, the model recognised that a proportion of cycles are cancelled and therefore may incur less costs. 2018-19 data from a personal communication with the HFEA was used to estimate the proportion of treatment cycles to attribute lower costs to arising from cancellation. These data are summarised in Table 49.

Table 48: Model intervention costs

Intervention	Cost	Source
Expectant management	£0.00	Guideline committee
IUI without OS	£632	National Schedule of NHS Costs 2021-22 [a]
Clomifene citrate + IUI	£633.70	National Schedule of NHS Costs 2021-22 and BNF [b]
Letrozole/anastrozole + IUI	£632.86	National Schedule of NHS Costs 2021-22 and BNF [c]

Intervention	Cost	Source
Gonadotropins + IUI	£1,481	National Schedule of NHS Costs 2021-22 [d]
IVF	£3,649	2023-25 NHS Payment Scheme (amended) (https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/#heading-2) [e]
IVF cancelled pre-harvest	£1,224	NICE 2013 (CG156) and PSSRU Unit Costs Manual 2023 (https://www.pssru.ac.uk/unitcostsreport/#tabs_desc_10_2) [f]
IVF cancelled post-harvest	£3,140	Maheshwari 2010, NICE 2013 (CG156) and PSSRU Unit Costs Manual 2023 (https://www.pssru.ac.uk/unitcostsreport/#tabs_desc_10_2) [g]

(a) Currency description - Intrauterine Insemination without Superovulation; Currency code - MC09Z; Based on total HRG
(b) BNF accessed August 2024 (https://bnf.nice.org.uk/drugs/clomifene-citrate/medicinal-forms/#oral-tablet); 5 doses of clomifene citrate 50mg at £0.34 per tablet plus cost of IUI without Superovulation
(c) BNF accessed August 2024 (https://bnf.nice.org.uk/drugs/letrozole/medicinal-forms/); 5 doses of Letrozole 2.5mg tablets at £0.17 per tablet plus cost of IUI without Superovulation
(d) Currency description - Intrauterine Insemination with Superovulation; Currency code – MC07Z; Based on total HRG which consists entirely of outpatient procedures
(e) Price to include 1 fresh and 1 frozen cycle
(f) Cost from CG156 updated to 2022-23 prices using the NHSCII and HCHS inflation indices
(g) Cost from CG156 updated to 2022-23 prices using the NHSCII and HCHS inflation indices
IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Table 49: Proportion of cycles cancelled by treatment stage, 2018-19

Patient age (years)	Cycles cancelled at or before egg collection	Fresh embryo transfer cycles cancelled following egg collection	Cycles cancelled following egg/embryo thaw
18-36	4.1%	6.0%	1.7%

(a) Note to this data supplied by the HFEA: This data includes only NHS-funded IVF cycles begun with the intention of creating a pregnancy in 2018/19. Cycles cancelled at or before egg collection refers to the proportion of egg collections planned, and either abandoned or completed without collecting eggs. Fresh embryo transfer cycles cancelled following egg collection refers to the proportion of cycles with eggs collected but no subsequent embryos transferred. Cycles in which embryos were created, some were stored and/or donated, none were transferred, and some may have been discarded are excluded from this field. Cycles cancelled following egg/embryo thaw refers to the proportion of cycles in which an egg or embryo was thawed, but no embryo subsequently transferred. This data is from a live register and may not match data provided in previous requests or published elsewhere. One treatment centre has been excluded due to data quality issues.

The model also accounted for “downstream” costs related to birth, multiples in particular, and complications arising from OHSS. Differences in live birth rates between the intervention strategies will have implication costs. As fertility treatment is associated with higher multiple birth rates it was important to capture the additional costs that would be incurred by the NHS from the different strategies. However, as the NHS routinely provides treatment and care for births that were spontaneously conceived a decision was made not to include the cost of singleton births in the base case analysis. Therefore, the cost of a multiple birth in the base case analysis was the incremental cost of a twin birth (for which there is more cost data) compared to a singleton birth. So that this incremental cost can be estimated the costs of both singleton, and twin births are included as input parameters. The model is constructed so that singleton costs can be included as part of a sensitivity analysis in which case the multiple birth cost would be based on the absolute cost value for this input. The model inputs related to birth and OHSS costs are reported in Table 50.

Table 50: Birth and OHSS costs

Outcome	Cost	Source
OHSS moderate	£1,274	Maheshwari 2010, NICE 2013 (CG156) and PSSRU Unit Costs Manual 2023 (https://www.pssru.ac.uk/unitcostsreport/#tabs_desc_10_2) [a]
OHSS severe	£3,873	Maheshwari 2010, NICE 2013 (CG156) and PSSRU Unit Costs Manual 2023 (https://www.pssru.ac.uk/unitcostsreport/#tabs_desc_10_2) [a]
Singleton birth	£5,903	Jacklin and Marceniuk (2018) [b]
Multiple birth	£16,846	Jacklin and Marceniuk (2018) [b]

(a) Cost from CG156 updated to 2022-23 prices using the NHSCII and HCHS inflation indices
(b) https://www.hfea.gov.uk/media/2712/nga-twin-pregnancy-costing-final.pdf and updated to 2022-23 prices using the NHSCII
OHSS: ovarian hyperstimulation syndrome

Health state utilities and QALYs

In accordance with the NICE reference case, an annual discount rate of 3.5% was applied to health state utilities accrued. Whilst the relationship between health-related quality of life and infertility is complex there is evidence to suggest that there are short term effects on mental health, depression and anxiety in particular, and longer-term effects on more general measures of well-being (Skedgel 2023).

Deriving health state utilities for live birth is not straightforward. A systematic literature review was conducted to search for potential quality of life inputs and/or approaches to be used for the health economic model. The quality-of-life (QoL) search strategy can be found in Appendix B. A total of 1,584 items were identified after duplicate papers had been removed. Of these 1,584 studies, 33 papers were ordered for full text review. For the 33 papers included for the full text review, these studies were initially categorised by outcome. These outcomes were:

- 36-item Short Form Survey (SF-36) – 11 papers
- 12-item Short Form Survey (SF-12) – 2 papers
- Willingness to pay (WTP) – 10 papers
- Other (defined as any other utility outcome not listed as above or health economic analyses where it was not clear how QoL had been captured) – 8 papers

Within this categorisation process, studies could also be excluded if upon full text review it was clear that no utility data was reported (2 papers).

As in line with the NICE reference case, it was decided from the outset that the preference for capturing QoL in the base case analysis would be to measure outcomes with Quality-Adjusted Life-Years (QALYs) – using EQ-5D values – as this approach allows for comparability and consistency with other health economic evaluations. It was however decided that in the absence of EQ-5D data other utility values could be used. In addition, other approaches to assess cost effectiveness could be used in sensitivity analyses if appropriate.

Following the initial categorisation of studies, studies were judged based on their applicability. Applicability was determined based on the population under review, and if appropriate, the intervention being assessed and the suitability of utility values (if reported). Because SF-36 and SF-12 values can be easily mapped to EQ-5D utility values these studies were assessed for their applicability first. Based on applicability alone 5 of the 11 SF-36 papers were excluded and 1 of the 2 SF-12 studies was excluded. The remaining 6 SF-36

papers and 1 SF-12 paper were subsequently assessed more comprehensively – assessing applicability and methodological quality.

In conjunction with this, the WTP studies and 'Other' studies were assessed for applicability. When assessing the WTP and 'Other' studies the primary objective was to determine if the reported values in the studies could be mapped to a utility value. Based on this criterion, and applicability concerns, 4 of the 10 WTP studies and 6 of the 8 'Other' studies were excluded.

This resulted in a total of 15 studies (6 SF-36, 1 SF-12, 6 WTP and 2 'Other' studies) being assessed more comprehensively (Agostini 2017, Ahmadi 2014, Ashraf 2015, Botha 2018, Fenwick 2023, El Kissi 2014, Gambadauro 2023, Kato 2021, Keller 2023, Krol 2019, Milman 2017, Ragni 2005, Scotland 2011, Sezgin 2016, Skedgel 2021). Brief study descriptions, outcomes and judgement on applicability and methodology were summarised for each of these 15 studies to allow for comparison of the most appropriate study (if any) to be employed within the health economic model. Based on this qualitative analysis it was agreed that the most appropriate approach for measuring health state utility associated with a live birth was to use the same approach as the last NICE guideline (CG156) – based on the data reported in Scotland 2011. Of note, this study was identified in the QoL sift. The approach for capturing QoL is detailed below.

Any health state utility gain had to relate to a couple or person seeking treatment and not any, as yet unconceived life. In the base case analysis this utility gain was limited to the person giving birth but possible impacts on partner health-related quality of life were explored in a sensitivity analysis. It was assumed that any gain in health-related quality of life resulting from a live birth would persist for the remainder of the woman's life, estimated at 53 years from ONS 2020-22 lifetables (ONS 2024) for the base case analysis. Although this could potentially over-estimate the overall QALY gain from a live birth it will be mitigated by the heavy discounting of health state utilities in later years of life. The model uses the same health state utility gain for a live birth as was used in the previous guideline (NICE 2013). A health state utility loss was also applied for occurrences of moderate and severe OHSS. As no published health state utility values was found for these health states, they were proxied by using values for moderate and severe pain respectively. The model assumed a duration of 2 weeks for OHSS symptoms although 7-10 days is more typical (RCOG 2016). The model makes the simplifying assumption that there are no health state utility implications related to multiple birth over and above live birth more generally. This was because the most serious adverse outcomes associated with multiple birth and prematurity are more frequently experienced by the neonate than the mother and again this would involve estimating QALYs for an individual that did not exist at the point at which treatment is commenced.

The health state utilities used in the model are summarised in Table 51.

Table 51: Model health state utilities

Outcome	Health state utility gain	Duration	Source
OHSS moderate	-0.084	14 days	Devlin 2018 [a]
OHSS severe	-0.276	14 days	Devlin 2018 [b]
Live birth	0.070	Lifelong	Scotland 2011

(a) Based on an EQ-5D-5L value set for England and using moderate pain as a proxy for moderate OHSS
(b) Based on an EQ-5D-5L value set for England and using severe pain as a proxy for severe OHSS
OHSS: ovarian hyperstimulation syndrome

An illustrative cost-effectiveness threshold of £30,000 per QALY was used to assess cost-effectiveness which is reflected in the results section, although cost-effectiveness acceptability curves (CEAC) were produced for probabilistic analyses which allows cost-effectiveness at alternative thresholds to be assessed. Whilst this threshold is greater than the £20,000 per QALY suggested as a benchmark criteria for assessing cost-effectiveness in

"NICE: Our Principles" the committee believed that the QALY did not fully capture other non-HRQoL benefits of fertility treatment and that huge uncertainty existed with respect to both the method and valuation of treatment benefits. Other authors have also suggested that QALY approaches do not fully capture the benefits of fertility treatment (Keller 2022, Skedgel 2023).

Sensitivity analysis

In addition to deterministic analysis, where model results are presented for model input point estimates, probabilistic sensitivity analysis was also undertaken to assess and quantify the uncertainty around model estimates of cost-effectiveness. This involved running a total of 10,000 Monte Carlo simulations where, with the exception of some deterministic parameters, model inputs are sampled from a probability distribution. In each simulation the costs and QALYs are calculated for strategy.

However, uncertainty in the model is not limited to sampling error and therefore a number of sensitivity analyses, both deterministic and probabilistic, were undertaken which involve changes to the assumptions or inputs used in the base case assessment. These are summarised below:

i. As per base case but with baseline expectant management births based on Bhattacharya 2008
ii. As per base case but with depletion of susceptibles
iii. As per base case but with depletion of susceptibles and with baseline expectant management births based on Bhattacharya 2008
iv. As per the base case but varying the time horizon of the model
v. As per the base case but varying health state utility from a live birth
vi. As per the base case but varying the age at which treatment is started
vii. As per the base case but including singleton costs in the analysis
viii. As per the base case but varying treatment costs of IUI without ovarian stimulation
ix. As per the base case but varying the treatment costs of IVF

Results

Base case analysis

Table 52 shows the deterministic results of the base case analysis assessed using a cost-effectiveness threshold of £30,000 per QALY, with the breakdown of costs and QALYs indicated in Table 53 and Table 54 respectively. The results are graphed on a cost-effectiveness plane in Figure 32.

In Table 52 incremental costs and incremental QALYs are calculated relative to the next best non-dominated strategy which allows an incremental cost-effectiveness ratio (ICER) to be computed. The strategy with the highest QALYs and an ICER below the cost-effectiveness threshold is considered the most cost-effective. The nZole + IUI | IVF strategy is said to be dominated as ClomC + IUI | IVF is both cheaper and more effective. ClomC + IUI | IVF and IUI without OS | IVF are both ruled out on grounds of extended dominance. This is because Gn + IUI | IVF is more effective and has a lower ICER than either of these strategies would have if calculated relative to the next non-dominated treatment. This leaves IVF and Gn + IUI | IVF as the only non-dominated strategies but as the ICER for Gn + IUI | IVF at £40,502 per QALY is above a cost-effectiveness threshold of £30,000 per QALY then it would not be considered as a cost-effective alternative to IVF.

The strategies are also compared in terms of their Net Monetary Benefit (NMB) which essentially utilises a rearrangement of the ICER formula to give the same but perhaps more intuitive result. The formula for the NMB is as follows:

NMB = QALYs x cost-effectiveness threshold – costs

The multiplication of QALYs by the cost-effectiveness threshold (£30,000 in Table 52) provides a valuation of the benefit of the strategy in monetary terms. The costs of the strategy are then deducted from this to provide an estimate of net benefit, and the most cost-effective strategy is the one with the highest NMB, which is IVF in this analysis.

Table 52: Cost-effectiveness results for the deterministic base case analysis

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,962	N/A	0.809	N/A	N/A	£14,316
ClomC + IUI | IVF	£11,384	N/A	0.838	N/A	Extended dominance	£13,743
nZole + IUI | IVF	£11,533	N/A	0.823	N/A	Dominated	£13,157
IUI without OS | IVF	£12,592	N/A	0.866	N/A	Extended dominance	£13,400
Gn + IUI | IVF	£13,824	£3,862	0.905	0.096	£40,502	£13,315

ClomC: clomifene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Table 53: Cost breakdown for deterministic base case analysis

Intervention	Treatment costs	OHSS costs	Twin costs	Total costs
IVF	£9,691	£109	£162	£9,962
ClomC + IUI | IVF	£10,894	£247	£243	£11,384
nZole + IUI | IVF	£11,052	£250	£231	£11,533
IUI without OS | IVF	£12,017	£320	£255	£12,592
Gn + IUI | IVF	£13,292	£235	£296	£13,824

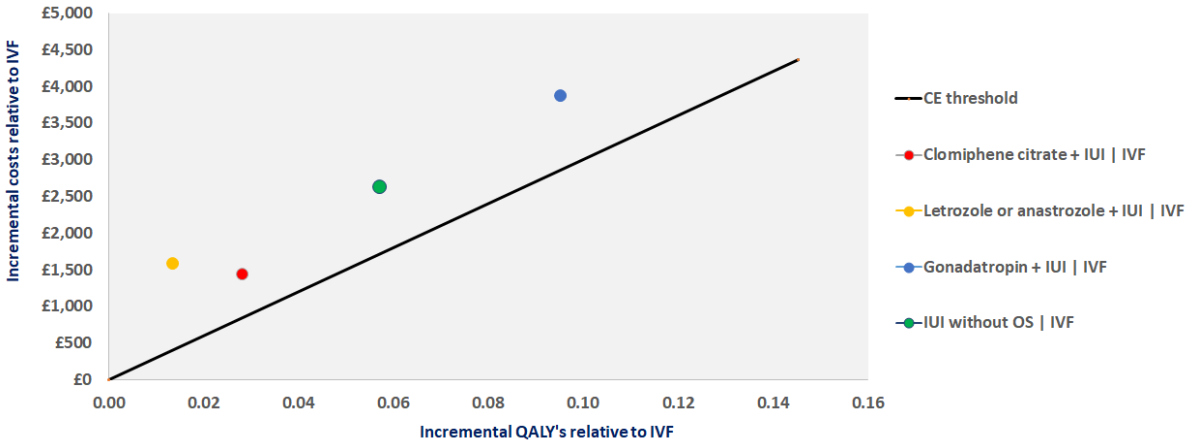
ClomC: clomipfene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; nZole: anastrozole/letrozole; OHSS: ovarian hyperstimulation syndrome; OS: ovarian stimulation

Table 54: QALY breakdown for deterministic base case analysis

Intervention	OHSS QALYs	Live Birth QALYs	Total QALYs
IVF	-0.00029	0.810	0.809
ClomC + IUI | IVF	-0.00066	0.838	0.838
nZole + IUI | IVF	-0.00067	0.824	0.823
IUI without OS | IVF	-0.00086	0.867	0.866
Gn + IUI | IVF	-0.00063	0.905	0.905

ClomC: clomifene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; nZole: anastrozole/letrozole; OHSS: ovarian hyperstimulation syndrome; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 32: Cost-effectiveness plane for deterministic base case analysis



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

A total of 10,000 Monte Carlo simulations were run for the base case analysis in order to give an indication of the uncertainty around the point estimates reported in the deterministic sensitivity analysis. The results of these simulations are reported in Table 55.

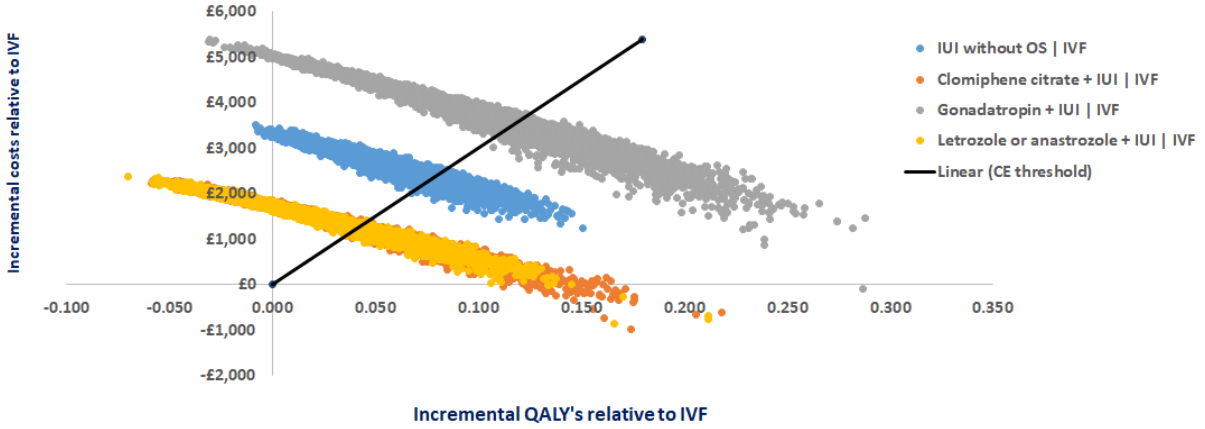
Table 55: PSA for the base case analysis

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,929	0.818	N/A	£14,616 (£10,281 to £20,639)	55%	74%
ClomC + IUI | IVF	£11,296	0.850	Extended dominance	£14,194 (£8,117 to £20,665)	16%	17%
nZole + IUI | IVF	£11,449	0.835	Dominated	£13,604 (£7,960 to £22,325)	3%	3%
IUI without OS | IVF	£12,539	0.875	Extended dominance	£13,725 (£6,508 to £22,721)	7%	1%
Gn + IUI | IVF	£13,728	0.915	£39,124	£13,730 (£7,687 to £21,402)	18%	4%

(a) Using a cost-effectiveness threshold of £30,000 per QALY
(b) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectivebess ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life year

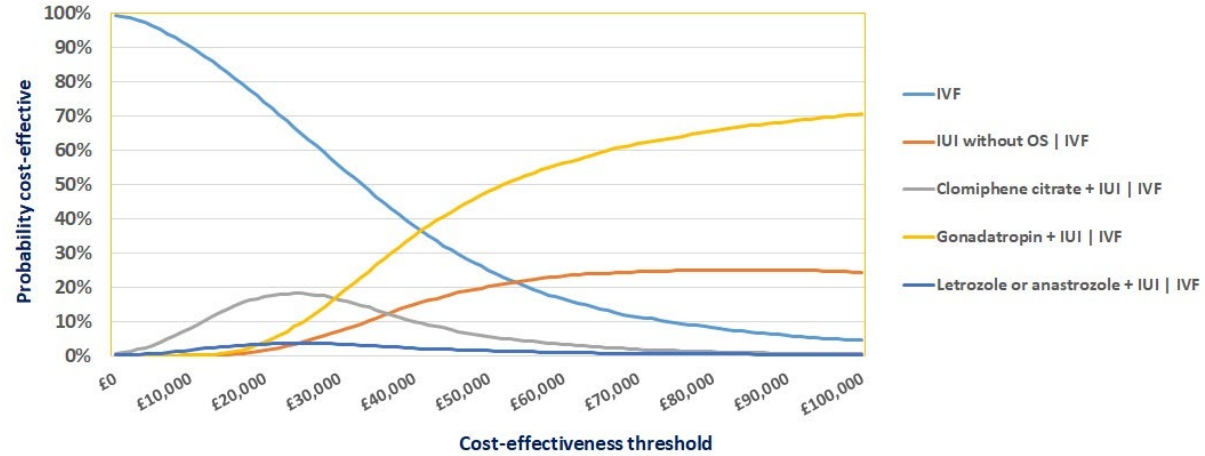
All 10,000 simulation are illustrated on the cost-effectiveness plane in Figure 33 and the cost-effectiveness acceptability curve, showing the probability each intervention is cost-effective at different cost-effectiveness thresholds, is shown at Figure 34.

Figure 33: Cost-effectiveness plane for the PSA of the base case analysis



CE: cost effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 34: CEAC for the base case analysis



CEAC: cost effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation

The PSA gives a very similar conclusion to the deterministic analysis with IVF being the strategy with the highest NMB, despite having the lowest QALY gain of all alternatives. Whilst the CEAC does suggest some uncertainty, IVF has a 55% probability of being the most cost-effective strategy at a cost-effectiveness threshold of £30,000 per QALY.

Sensitivity analysis

i. As per base case analysis but with baseline (expectant management) live births based on Bhattacharya 2008

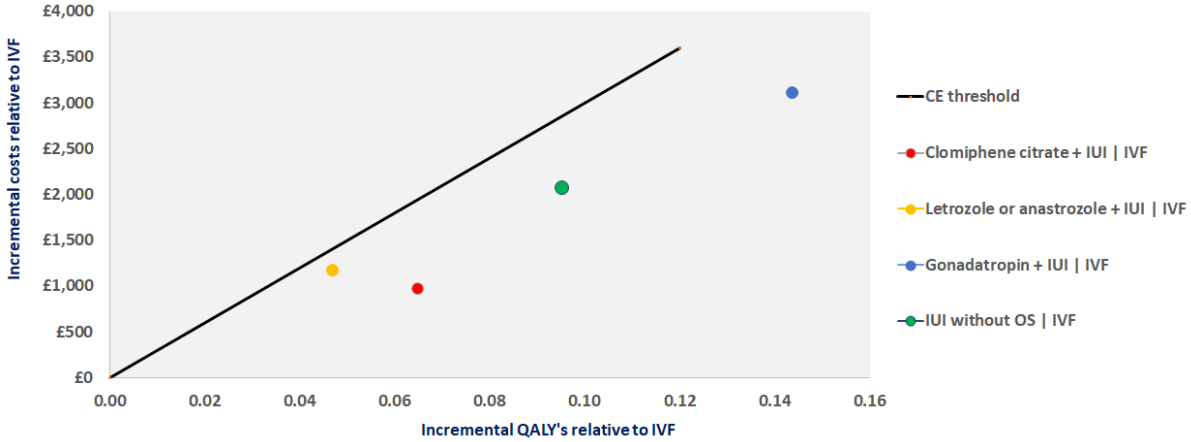
In this study the baseline expectant management births are estimated using a published study (Bhattacharya 2008) instead of the prediction model. The deterministic results of this sensitivity analysis are summarised in Table 56 and the cost-effectiveness plane in Figure 35. In this analysis strategies using IUI prior to IVF produces a higher NMB than IVF despite their higher cost. The most cost-effective strategy in Gn + IUI | IVF at a cost-effectiveness threshold of £30,000 per QALY although ClomC + IUI | IVF would be preferred if a lower cost-effectiveness threshold of £20,000 per QALY was employed.

Table 56: Deterministic cost-effectiveness analysis as per the base case analysis but with baseline live births based on Bhattacharya 2008

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,665	N/A	0.904	N/A	N/A	£17.453
ClomC + IUI | IVF	£10,627	£962	0.969	0.065	£14,815	£18,439
nZole + IUI | IVF	£10,826	N/A	0.951	N/A	Dominated	£17,703
IUI without OS | IVF	£11,743	N/A	0.999	N/A	Extended dominance	£18,229
Gn + IUI | IVF	£12,767	£2,140	1.048	0.079	£27,079	£18,670

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 35: Cost-effectiveness plane as for base case analysis but with baseline live births based on Bhattacharya 2008



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

Table 57 summarises the output of 10,000 probabilistic simulations of the model with all simulations plotted on the cost-effectiveness plane shown in Figure 36. The results again are consistent with the deterministic analysis. It shows that Gn + IUI | IVF is the most expensive strategy but also the most clinically effective strategy. It is also the most cost-effective using a £30,000 per QALY cost-effectiveness threshold with the highest NMB and an ICER that falls below the £30,000 per QALY threshold. However, as indicated by Table 57 and the CEAC in Figure 37 the cost-effectiveness is highly sensitive to the cost-effectiveness threshold, as at a cost-effectiveness threshold of £20,000 per QALY ClomC + IUI | IVF is the most cost-effective strategy with an ICER of £14,167 albeit with the same probability (33%) as IVF of being the most cost-effective option.

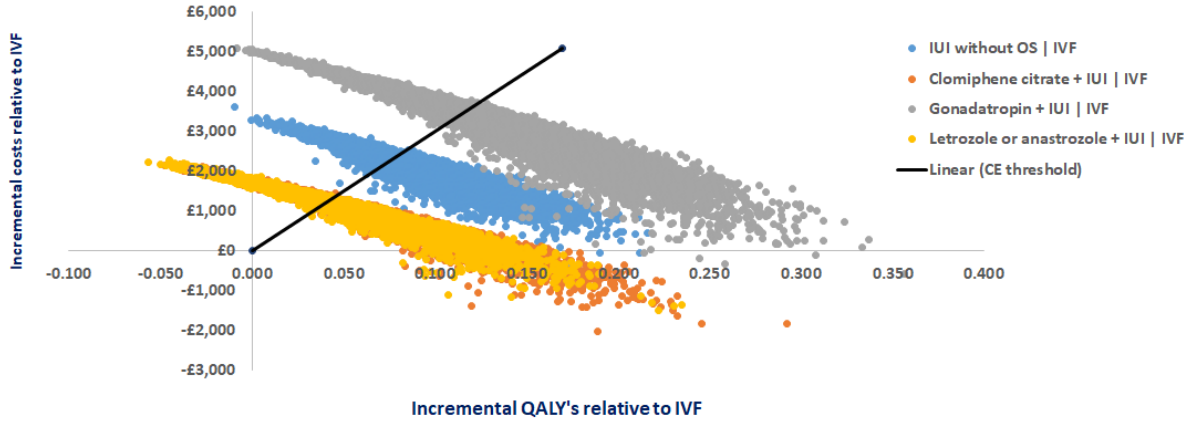
Table 57: PSA as per the base case analysis but with baseline live births based on Bhattacharya 2008

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,637	0.909	N/A	£17,622 (£11,544 to £25,084)	17%	33%
ClomC + IUI | IVF	£10,556	0.974	£14,167	£18,649	18%	33%

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
				(£10,273 to £27,188)		
nZole + IUI | IVF	£10,759	0.956	Dominated	£17,916 (£10,047 to £28,637)	4%	7%
IUI without OS | IVF	£11,712	1.001	Extended dominance	£18,314 (£8,955 to £29,448)	24%	14%
Gn + IUI | IVF	£12,715	1.048	£28,806	£18,738 (£9,587 to £27,556)	37%	13%

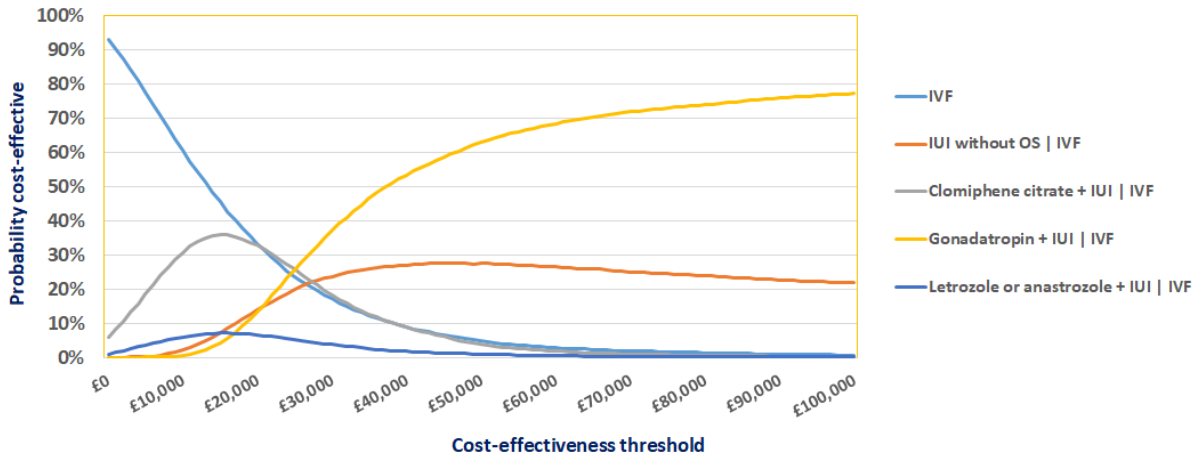
(c) Using a cost-effectiveness threshold of £30,000 per QALY
(d) Using a cost-effectiveness threshold of £20,000 per QALY
ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 36: PSA Cost-effectiveness plane but with baseline live births based on Bhattacharya 2008



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 37: CEAC as per the base case analysis but with baseline live births based on Bhattacharya 2008



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

ii. As per base case analysis but with an adjustment for the depletion of susceptibles

In this sensitivity analysis it was assumed that 2nd line treatment or expectant management following treatment would not be as effective as successful 1st line treatment, as this population would have a worse prognosis on average than the original treatment cohort, as those with a better prognosis were more likely to achieve a live birth with 1st line treatment. To model this "depletion of susceptible" effect it was assumed that 5% of the population going on to 2nd line treatment or expectant management after treatment had a zero chance of live birth. Although the use of 5% with a zero chance of live birth was a somewhat arbitrary figure, it was agreed as a reasonable estimate by the guideline committee.

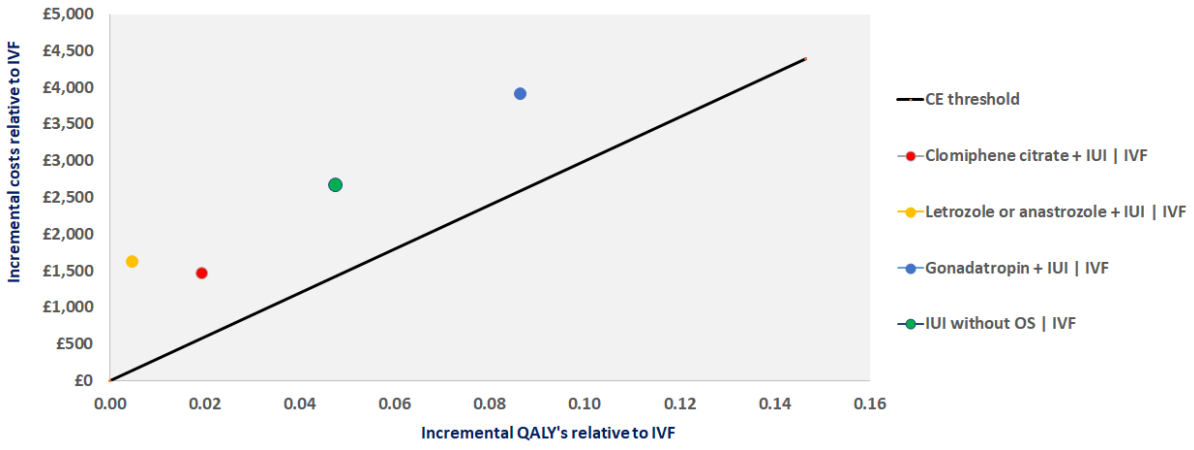
The deterministic results of this analysis are displayed in Table 58 and the cost-effectiveness plane, Figure 38. Compared with the base case analysis QALYs are reduced and costs, with the exception of the IVF strategy are increased. The result is that the cost-effectiveness of IVF is improved relative to the alternative interventions as indicated by the higher ICER of £45,006 per QALY for Gn + IUI | IVF.

Table 58: Deterministic cost-effectiveness analysis as per the base case analysis but with adjustment for depletion of susceptibles

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,960	N/A	0.782	N/A	N/A	£13,490
ClomC + IUI | IVF	£11,418	N/A	0.801	N/A	Extended dominance	£12,618
nZole + IUI | IVF	£11,567	N/A	0.787	N/A	Dominated	£12,032
IUI without OS | IVF	£12,627	N/A	0.829	N/A	Extended dominance	£12,248
Gn + IUI | IVF	£13,858	£3,643	0.868	0.078	£45,006	£12,191

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 38: Cost-effectiveness plane for deterministic analysis as per the base case analysis but with adjustment for the depletion of susceptibles



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; QALYs: quality-adjusted life years

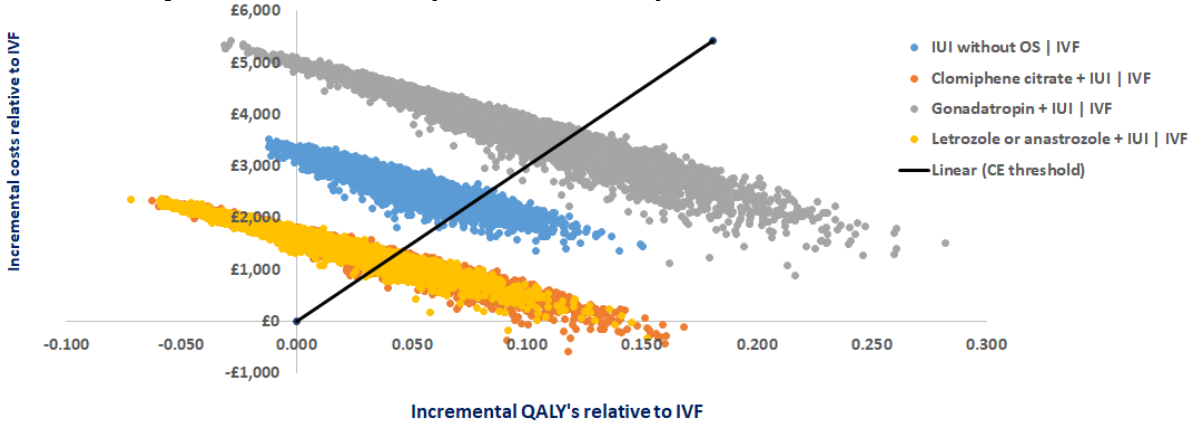
The increased cost-effectiveness of IVF relative to other interventions is also demonstrated in the PSA which is summarised in Table 59, and the cost-effectiveness plane showing all simulation results, Figure 39. The ICER of £43,675 per QALY for Gn + IUI | IVF relative to IVF is higher than the base case. The data and the CEAC, Figure 40, also show that the probability of IVF being most cost-effective at a cost-effectiveness threshold of £30,000 per QALY has risen to 65%, up from 55% in the base case analysis.

Table 59: PSA as per the base case analysis but with an adjustment for the depletion of susceptibles

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,930	0.790	N/A	£13,763 (£9,468 to £19,684)	65%	84%
ClomC + IUI | IVF	£11,340	0.812	Extended dominance	£13,011 (£7,300 to £19,089)	12%	12%
nZole + IUI | IVF	£11,491	0.797	Dominated	£12,427 (£7,048 to £20,803)	3%	2%
IUI without OS | IVF	£12,579	0.837	Extended dominance	£12,535 (£5,714 to £21,130)	4%	0%
Gn + IUI | IVF	£13,769	0.878	£43,675	£12,561 (£6,782 to £19,758)	16%	2%

(e) Using a cost-effectiveness threshold of £30,000 per QALY
(f) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

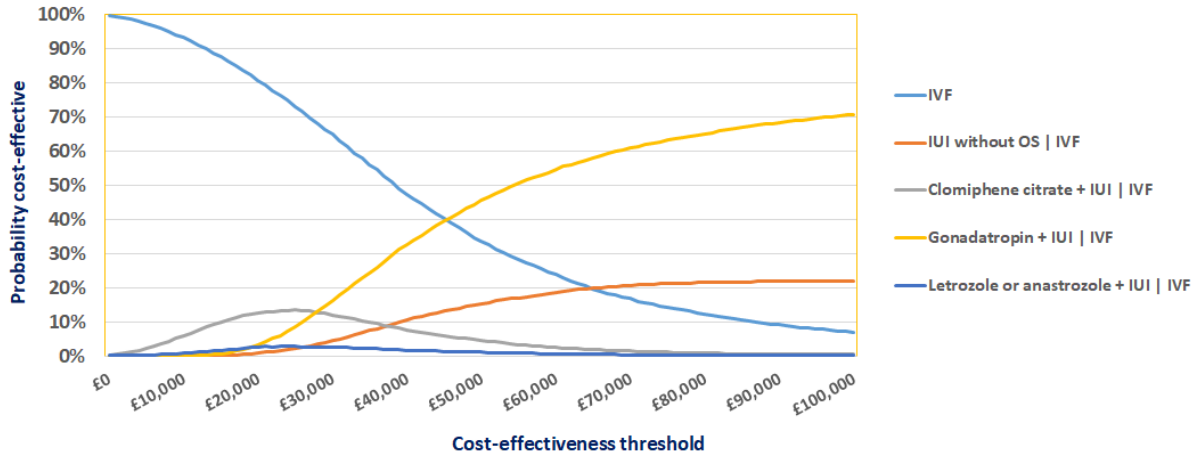
Figure 39: PSA Cost-effectiveness plane as per the base case but with an adjustment for the depletion of susceptibles



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

1

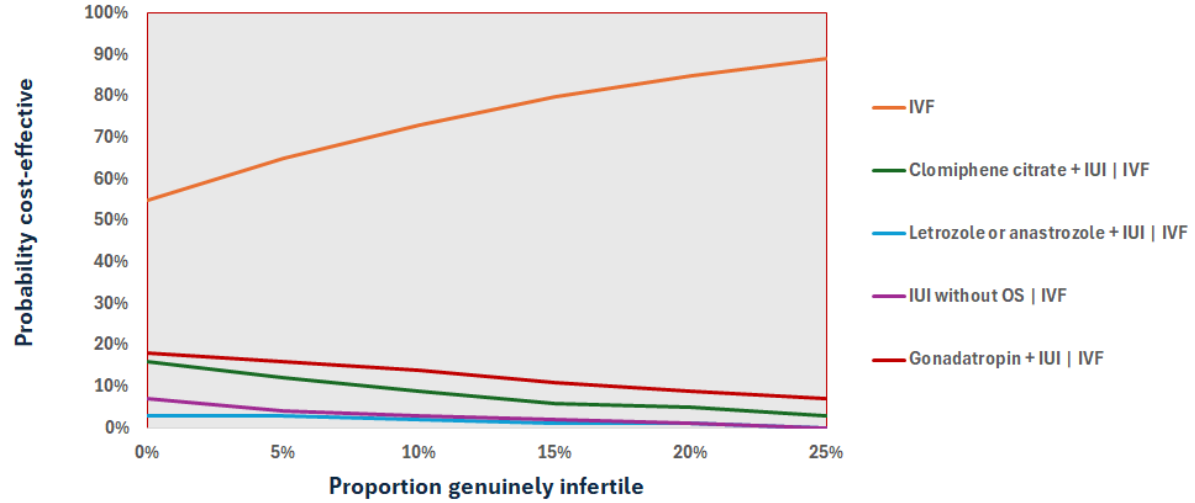
Figure 40: CEAC as per the base case but with an adjustment for the depletion of susceptibles



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Figure 41 shows the impact of varying the proportion who are genuinely infertile, and it shows that the probability of IVF being cost-effective increases the greater the depletion of susceptibles effect (as proxied by an increasing infertile proportion).

Figure 41: Graph to show impact of varying proportion who are genuinely infertile when taking into account depletion of susceptibles



IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

2 iii. As per base case but making an adjustment for depletion of susceptibles and with
3 baseline expectant management births based on Bhattacharya 2008

4

5 In this sensitivity analysis two changes are made to the base case analysis, with adjustment
6 made for depletion of susceptibles (using a 5% genuinely infertile proportion in those
7 unsuccessful with 1st line treatment) and with baseline expectant management live births

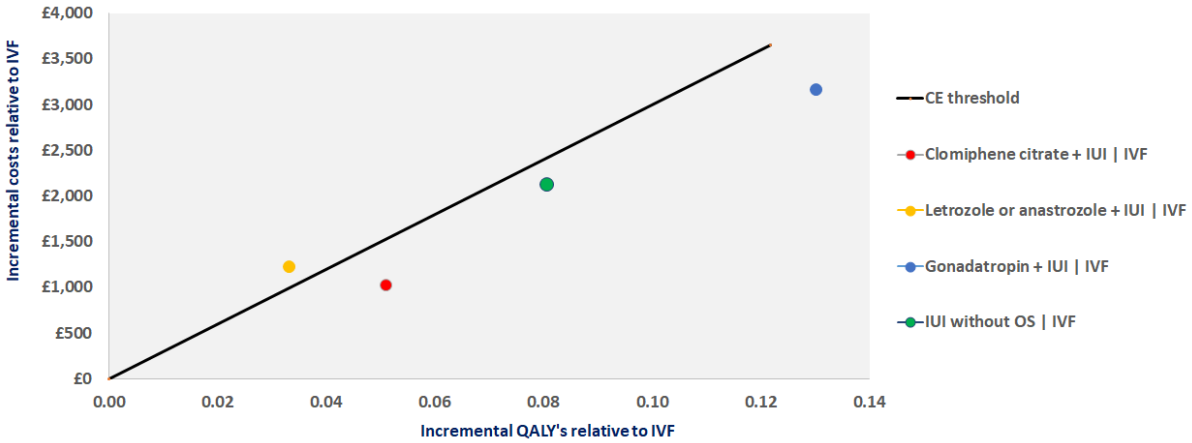
based on a published study (Bhattacharya 2008). The deterministic results are given in Table 60 and illustrated graphically on the cost-effectiveness plane in Figure 42. It shows that Gn + IUI | IVF is the most cost-effective option at a cost-effectiveness threshold of £30,000 per QALY, with a slightly higher NMB than IVF and with an ICER of £27,079 per QALY that falls beneath the threshold.

Table 60: Deterministic cost-effectiveness analysis as per the base case analysis but making an adjustment for the depletion of susceptibles and with baseline expectant management births based on Bhattacharya 2008

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,663	N/A	0.876	N/A	N/A	£16,627
ClomC + IUI | IVF	£10,675	£1,012	0.928	0.052	£19,741	£17,153
nZole + IUI | IVF	£10,875	N/A	0.910	N/A	Dominance	£16,416
IUI without OS | IVF	£11,793	N/A	0.958	N/A	Extended dominance	£16,914
Gn + IUI | IVF	£12,815	£2,140	1.007	0.079	£27,079	£17,384

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 42: Cost-effectiveness plane for deterministic analysis as per the base case analysis but with adjustment for the depletion of susceptibles and with baseline expectant management births based on Bhattacharya 2008



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

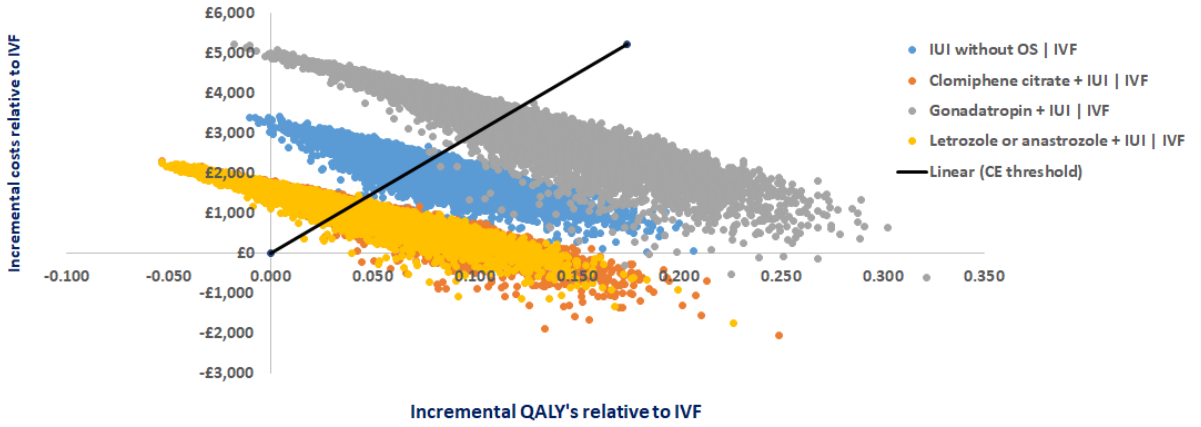
In the PSA simulations which are graphed in Figure 43, Gn + IUI | IVF emerges as the intervention with the highest mean NMB of £17,494 (Table 61). However, as indicated in Table 61 and the CEAC depicted in Figure 44, there is considerable uncertainty as to whether IVF or Gn + IUI | IVF is the most cost-effective strategy with those interventions having a 37% chance and 24% chance respectively of being the most cost-effective strategy when utilising a cost-effectiveness threshold of £30,000 per QALY.

Table 61: PSA as per the base case analysis but with an adjustment for the depletion of susceptibles and with baseline expectant management births based on Bhattacharya 2008

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,630	0.882	N/A	£16,841 (£10,694 to £24,631)	24%	43%
ClomC + IUI | IVF	£10,604	0.933	£19,349	£17,377 (£9,404 to £25,855)	16%	27%
nZole + IUI | IVF	£10,803	0.915	Dominated	£16,659 (£9,067 to £27,264)	3%	6%
IUI without OS | IVF	£11,749	0.960	Extended dominance	£17,058 (£8,146 to £28,002)	20%	11%
Gn + IUI | IVF	£12,754	1.008	£28,454	£17,494 (£8,584 to £26,258)	37%	13%

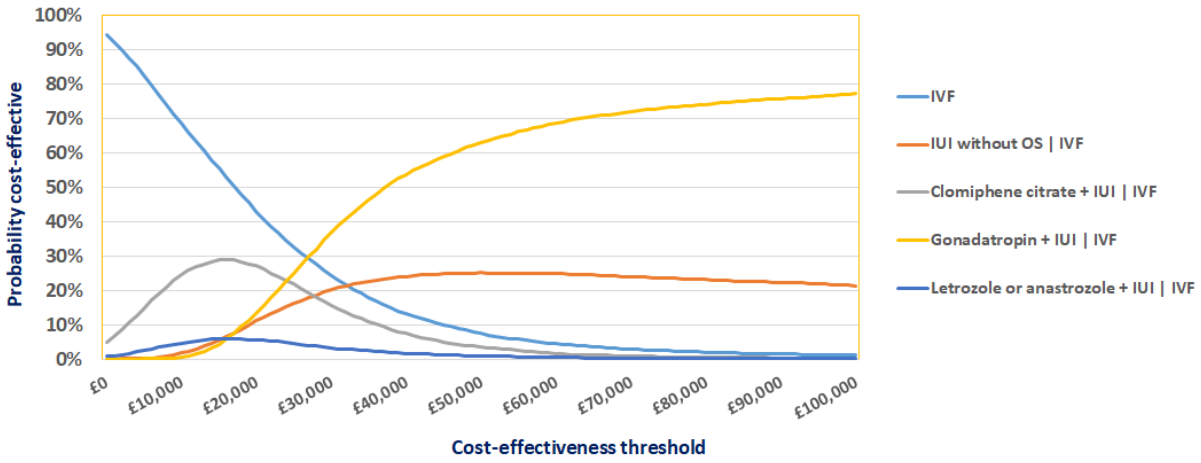
(g) Using a cost-effectiveness threshold of £30,000 per QALY
(h) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 43: PSA cost-effectiveness plane for deterministic analysis as per the base case analysis but with adjustment for the depletion of susceptibles and with baseline expectant management births based on Bhattacharya 2008



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 44: CEAC as per the base case but with an adjustment for the depletion of susceptibles and with baseline expectant management births based on Bhattacharya 2008



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

iv. Base case but varying the time horizon of the model

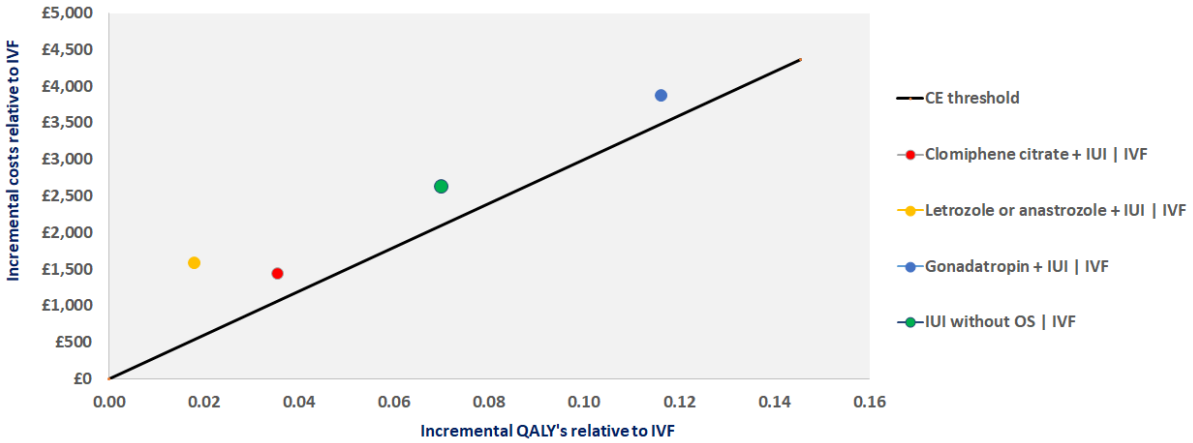
In this sensitivity analysis a shorter 36 month time horizon is used and the deterministic results are summarised in Table 62 and the cost-effectiveness plane in Figure 45. As per the base case analysis IVF continues to be the most cost-effective with the highest NMB of £8,379. The only non-dominated alternative Gn + IUI | IVF has an ICER of £33,202 which would not be considered cost-effective using a cost-effectiveness threshold of £30,000 per QALY.

Table 62: Deterministic cost-effectiveness analysis as per the base case but with a 36-month time horizon for cumulative live birth

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,946	N/A	0.611	N/A	N/A	£8,379
ClomC + IUI | IVF	£11,368	N/A	0.646	N/A	Extended dominance	£8,027
nZole + IUI | IVF	£11,517	N/A	0.629	N/A	Dominated	£7,352
IUI without OS | IVF	£12,577	N/A	0.681	N/A	Extended dominance	£7,847
Gn + IUI | IVF	£13,809	£3,864	0.727	0.116	£33,202	£8,006

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 45: Cost-effectiveness plane for the base case but with a 36-month time horizon for cumulative live birth



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

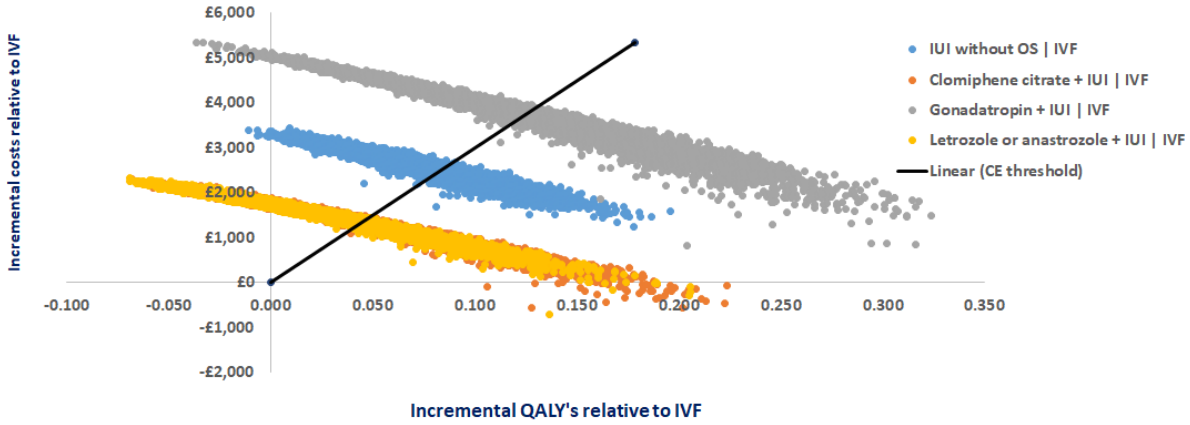
The PSA reinforces the deterministic results although it also shows that the conclusion that IVF is the most cost-effective option is less clear cut with the probability that IVF is most cost-effective falling from 55% in the base case analysis to 43% at a cost-effectiveness threshold of £30,000 per QALY. The PSA results are summarised in Table 63, the plot of simulations results in Figure 46 and the CEAC in Figure 47.

Table 63: PSA as per the base case analysis with a 36-month time horizon for cumulative live birth

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,914	0.621	N/A	£8,717 (£3,544 to £15,729)	43%	66%
ClomC + IUI | IVF	£11,286	0.660	Extended dominance	£8,522 (£1,791 to £16,238)	12%	18%
nZole + IUI | IVF	£11,437	0.643	Dominated	£7,848 (£1,224 to £17,760)	3%	4%
IUI without OS | IVF	£12,526	0.691	Extended dominance	£8,213 (£106 to £18,698)	12%	3%
Gn + IUI | IVF	£13,714	0.740	£32,033	£8,476 (£837 to £16,724)	29%	9%

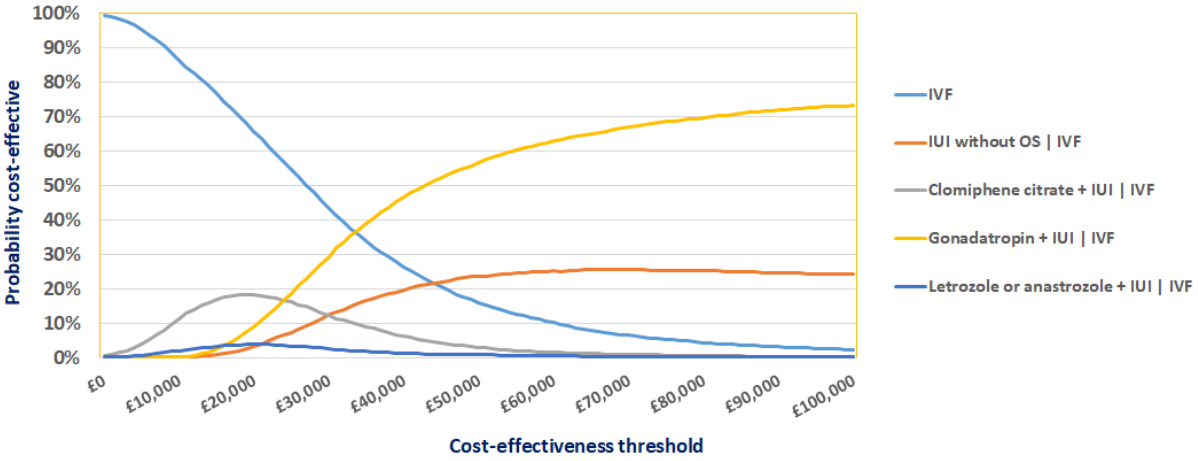
(i) Using a cost-effectiveness threshold of £30,000 per QALY
(j) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 46: PSA cost-effectiveness plane as per the base case analysis with a 36-month time horizon for cumulative live birth



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 47: CEAC as per the base case with a 36-month time horizon for cumulative live birth



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

Gn + IUI | IVF appears to be marginally more cost-effective than the IVF strategy when assessment is limited to a time horizon determined by the maximum treatment duration (14 months using model assumptions about the spacing of treatment cycles). QALYs are lower than in the base case reflecting a small-time horizon for spontaneous conception leading to live birth after completing treatment. Gn + IUI | IVF has a NMB that is £116 more than IVF in the deterministic analysis, with the complete results given in Table 64 and illustrated in Figure 48.

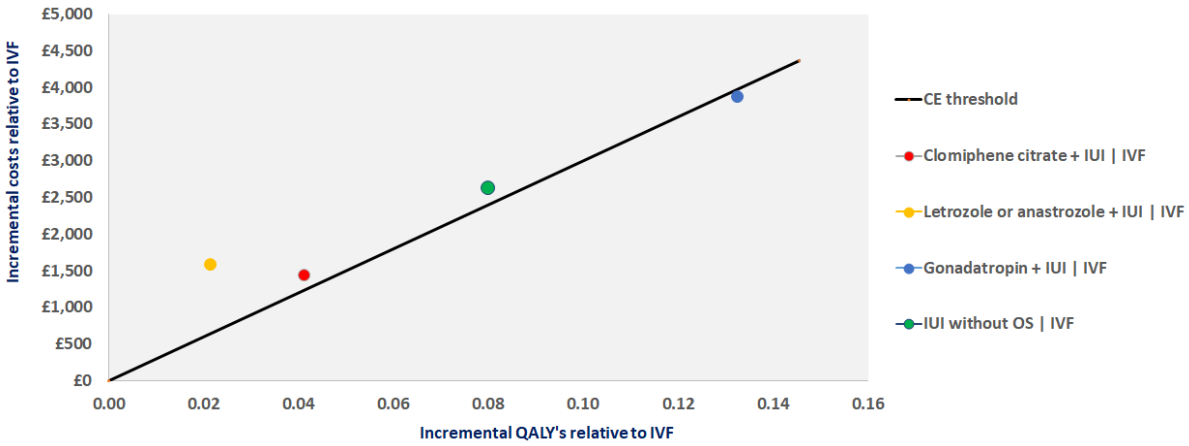
Table 64: Deterministic cost-effectiveness analysis as per the base case but with a maximum treatment duration time horizon for cumulative live birth

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,934	N/A	0.479	N/A	N/A	£4,427
ClomC + IUI | IVF	£11,537	N/A	0.520	N/A	Extended dominance	£4,247
nZole + IUI | IVF	£11,506	N/A	0.500	N/A	Dominated	£3,504

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IUI without OS | IVF	£12,567	N/A	0.559	N/A	Extended dominance	£4,193
Gn + IUI | IVF	£13,799	£3,865	0.611	0.132	£29,127	£4,543

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 48: Cost-effectiveness plane for the base case but with a maximum treatment duration time horizon for cumulative live birth



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

Further reducing the time horizon increases the uncertainty as to whether IVF or Gn + IUI | IVF is the most cost-effective strategy and, in the PSA, Gn + IUI | IVF has the highest mean NMB with similar probability of being cost-effective (37% v 35%) at a cost-effectiveness threshold of £30,000 per QALY. Summaries of this PSA are given in Table 65, Figure 49 and Figure 50.

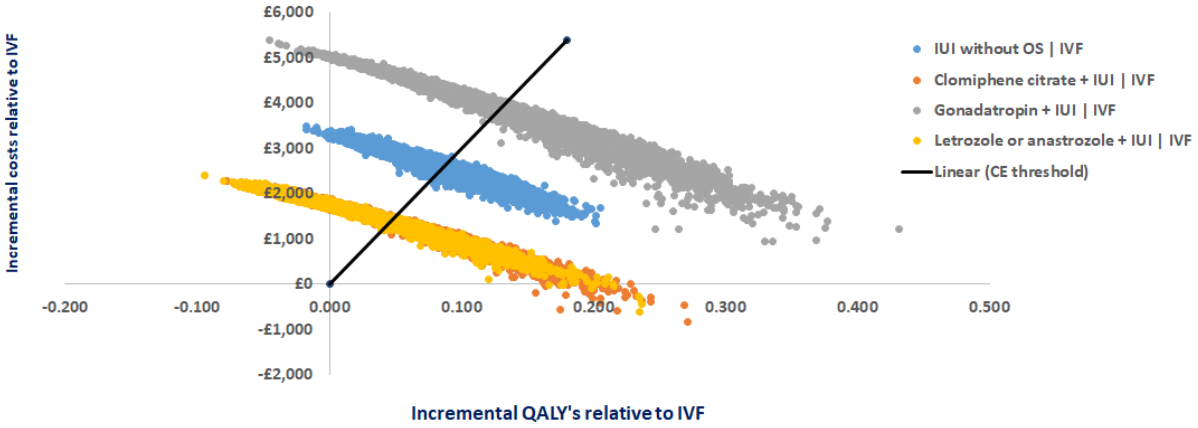
Table 65: PSA as per the base case analysis with a maximum treatment duration time horizon for cumulative live birth

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,904	0.490	N/A	£4,781 (-£946 to £12,346)	35%	58%
ClomC + IUI | IVF	£11,275	0.535	Extended dominance	£4,780 (-£2,596 to £13,445)	10%	18%
nZole + IUI | IVF	£11,428	0.515	Dominated	£4,031 (-£3,300 to £15,159)	2%	4%
IUI without OS | IVF	£12,514	0.570	Extended dominance	£4,591 (-£4,225 to £16,459)	16%	6%
Gn + IUI | IVF	£13,705	0.625	£28,048	£5,046 (-£3,731 to £14,100)	37%	14%

(k) Using a cost-effectiveness threshold of £30,000 per QALY

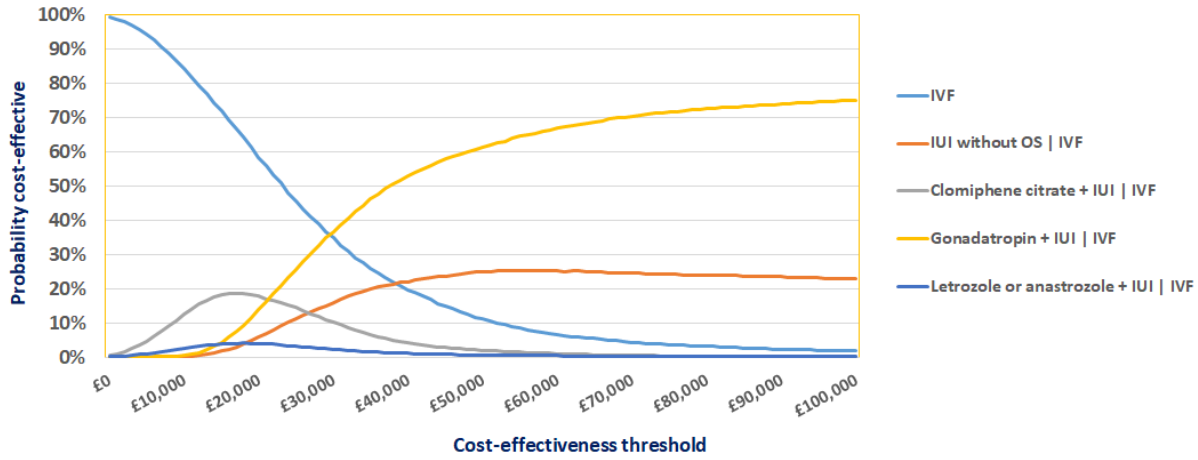
(l) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 49: PSA cost-effectiveness plane as per the base case with a maximum treatment duration time horizon for cumulative live birth



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 50: CEAC as per the base case with a maximum treatment duration time horizon for cumulative live birth



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

v. Base case but varying the health state utility from a live birth

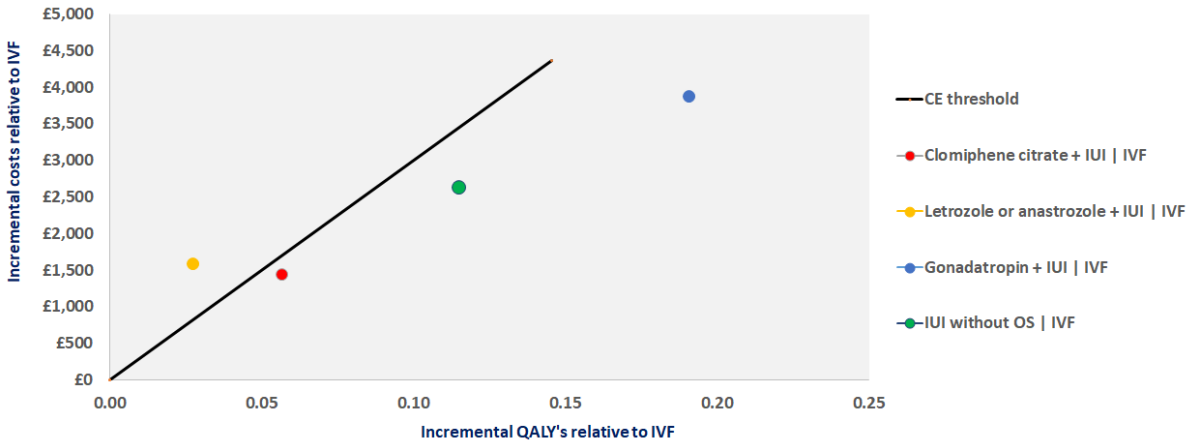
Table 66 and the cost-effectiveness plane in Figure 51 show the deterministic impact of a doubling of the utility gain from a live birth as might be considered appropriate, for example, if a partner's health related quality of life could also be impacted by subfertility. It shows that the cost-effectiveness of Gn + IUI | IVF is improved relative to the base case analysis with Gn + IUI | IVF the most cost-effective strategy at a cost-effectiveness threshold of £30,000 per QALY.

Table 66: Deterministic cost-effectiveness analysis as per the base case analysis with double the health state utility gain from a live birth

Intervention	Mean Costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER	NMB
IVF	£9,962	N/A	1.619	N/A	N/A	£38,604
ClomC + IUI | IVF	£11,384	N/A	1.676	N/A	Extended dominance	£38,889
nZole + IUI | IVF	£11,533	N/A	1.647	N/A	Dominated	£37,866
IUI without OS | IVF	£12,592	N/A	1.734	N/A	Extended dominance	£39,418
Gn + IUI | IVF	£13,824	£3,862	1.810	0.191	£20,215	£40,473

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 51: Cost-effectiveness plane as per the base case but with double the health state utility gain from a live birth



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

The results of the PSA are summarised in Table 67, the cost-effectiveness plane (Figure 52) and CEAC (Figure 53). Again, this reinforces the deterministic result that the cost-effectiveness of Gn + IUI | IVF is substantially improved compared to the base case utility gain assumption. At a cost-effectiveness threshold of £30,000 per QALY Gn + IUI | IVF has a far higher probability of being cost-effective (56%) than any other strategy. At a lower cost-effectiveness threshold of £20,000 per QALY then IVF strategy has the highest probability of being cost-effective (38%) but the conclusion as to whether IVF or Gn + IUI | IVF is the most cost-effective is quite finely poised.

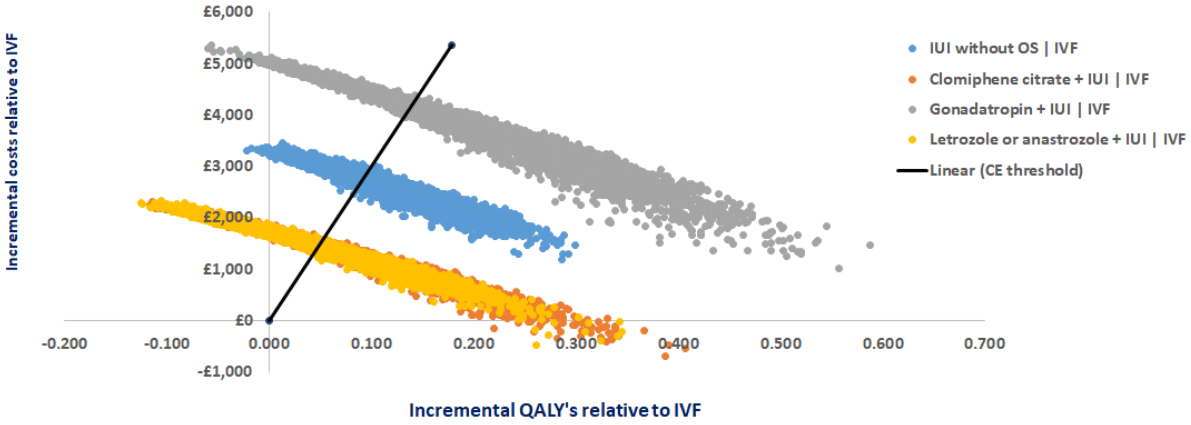
Table 67: PSA as per the base case analysis but with double the health state utility gain from a live birth

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,928	1.637	N/A	£39,187 (£30,833 to £50,256)	16%	38%
ClomC + IUI | IVF	£11,299	1.700	Extended dominance	£39,694 (£29,689 to £52,844)	3%	10%

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
nZole + IUI | IVF	£11,452	1.671	Dominated	£38,665 (£28,213 to £54,477)	1%	2%
IUI without OS | IVF	£12,535	1.753	Extended dominance	£40,046 (£28,208 to £57,266)	23%	15%
Gn + IUI | IVF	£13,729	1.831	£19,576	£41,211 (£27,652 to £52,862)	56%	35%

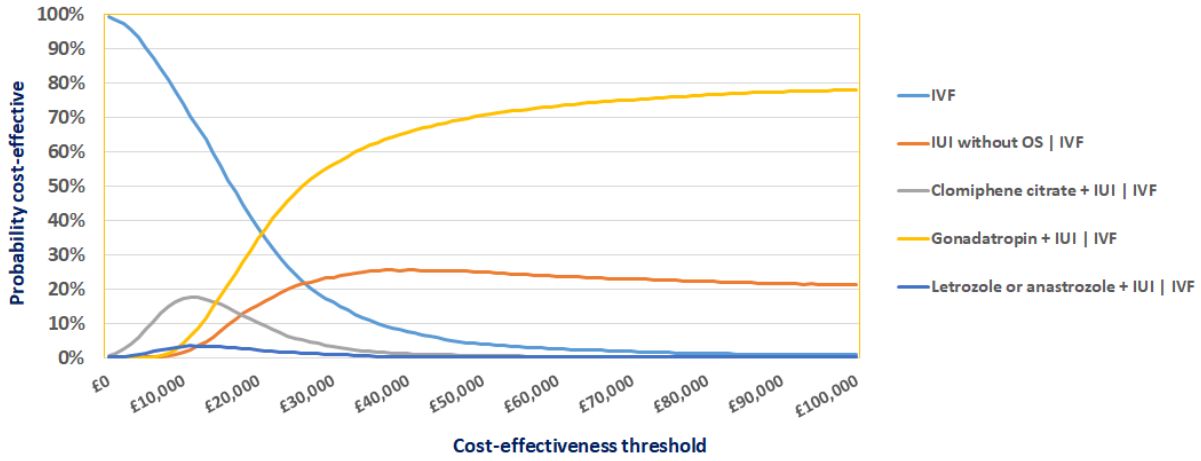
(m) Using a cost-effectiveness threshold of £30,000 per QALY
(n) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 52: PSA cost-effectiveness plane as per the base case but with double the health state utility gain from a live birth



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

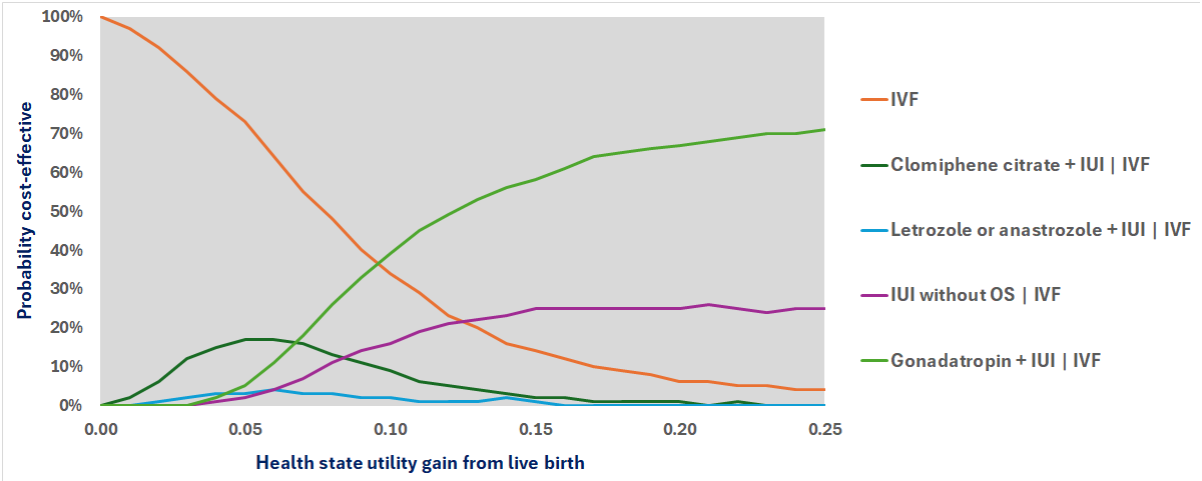
Figure 53: CEAC as per the base case but with double the health state utility gain from a live birth



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

PSA was repeated across different health state utility values to provide greater granularity on how cost-effectiveness of the different strategies varied with changes to assumptions about the health state utility gain arising from a live birth. This is graphed in Figure 54 and shows the probability of different strategies being cost-effective using a cost-effectiveness threshold of £30,000 per QALY. It suggests that at a health state utility gain from live birth of 0.10 or greater, Gn + IUI | IVF has the highest probability of being the most cost-effective treatment but that below that threshold IVF is likely to be the most cost-effective.

Figure 54: Graph to show impact of varying health state utility gain from a live birth

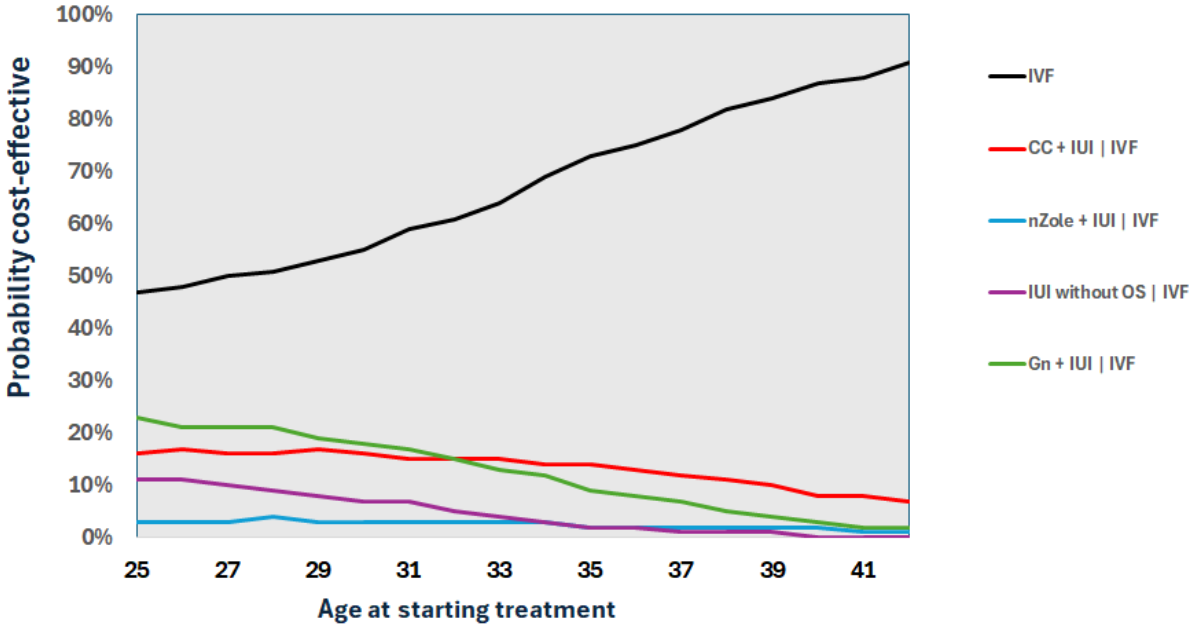


IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

vi. Base case but varying the age at which treatment is started

In this sensitivity analysis all model inputs and assumptions are maintained at their base case value except for the age at starting fertility treatment. It shows that IVF has an approximately 50% probability of being the most cost-effective at a cost-effectiveness threshold of £30,000 per QALY at an age of 25 years and that the probability rises continuously with increasing age.

Figure 55: Graph to show the impact of varying age at the start of treatment



CC: clomifene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; nZole: anastrozole/letrozole; OS: ovarian stimulation

vii. As per the base case but including singleton costs in the analysis

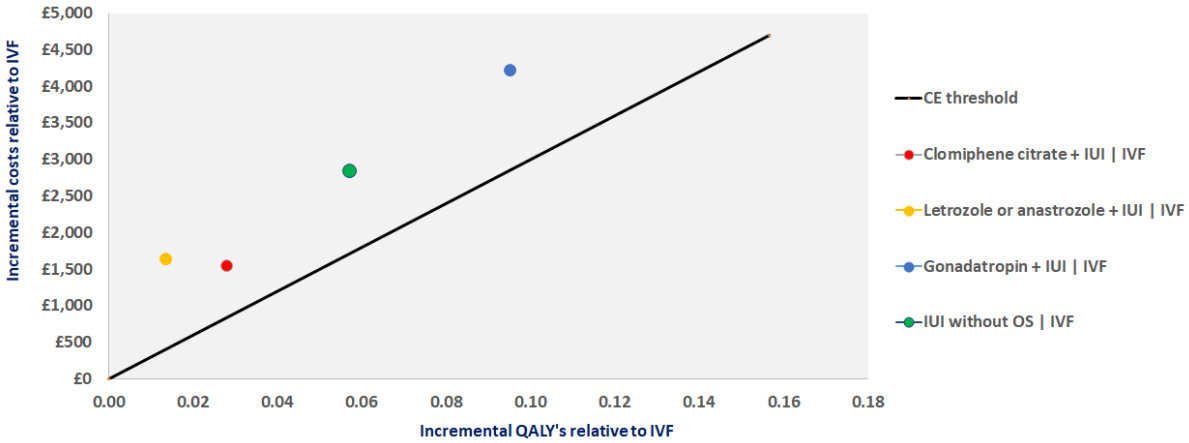
In this sensitivity analysis, the costs of singleton births were included as a "downstream" cost of fertility treatment. This has no bearing on the QALYs generated by the respective strategies but does increase total costs, with the greatest absolute effects occurring in those strategies that have higher cumulative live birth rates. However, as Table 68 and the cost-effectiveness plane in Figure 56 show, the overall cost-effectiveness conclusions are very similar to the base case. The NMB is reduced for all strategies reflecting higher costs and the ICER of the most clinically effective strategy rises to £44,057, strengthening slightly the conclusion that IVF is the most cost-effective strategy at a cost-effectiveness threshold of £30,000 per QALY.

Table 68: Deterministic cost-effectiveness analysis as per the base case analysis but including singleton costs

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£12,851	N/A	0.809	N/A	N/A	£11,427
ClomC + IUI | IVF	£14,382	N/A	0.838	N/A	Extended dominance	£10,745
nZole + IUI | IVF	£14,481	N/A	0.823	N/A	Dominated	£10,209
IUI without OS | IVF	£15,693	N/A	0.866	N/A	Extended dominance	£10,299
Gn + IUI | IVF	£17,052	£4,201	0.905	0.096	£44,057	£10,087

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 56: Cost-effectiveness plane as per the base case but including singleton costs



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

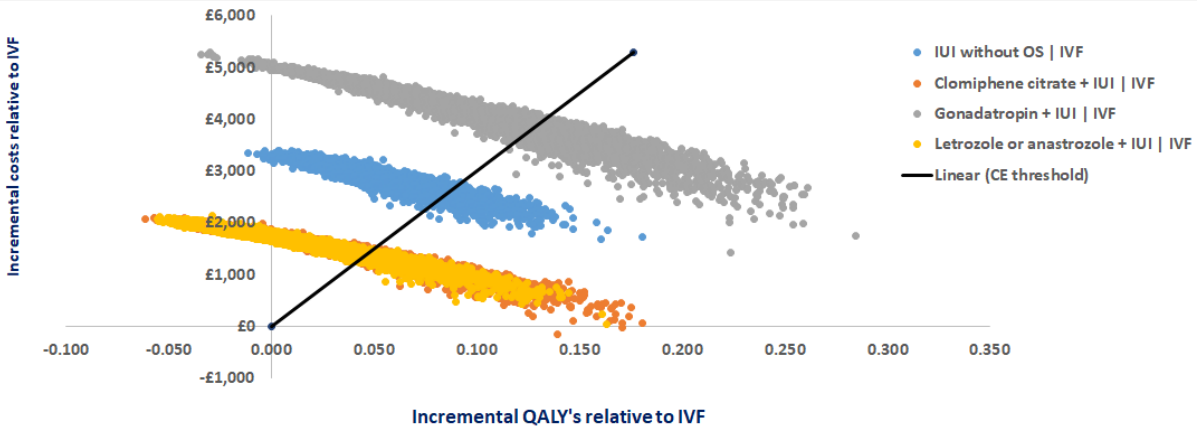
The results for the PSA are given in Table 69, the cost-effective plane plot of all 10,000 simulations in Figure 57 and the CEAC in Figure 58. As with the deterministic analysis the results do not differ markedly from the base case but the slight increase in the probability of IVF being the most cost-effective option at a cost-effectiveness threshold of £30,000 per QALY is reflected by the fact that the probability is the most cost-effective increases from 55% in the base case PSA to 63% in this analysis.

Table 69: PSA as per the base case analysis but including singleton costs

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£12,848	0.818	N/A	£11,683 (£7,795 to £16,690)	63%	81%
ClomC + IUI | IVF	£14,340	0.849	Extended dominance	£11,123 (£5,621 to £16,616)	17%	15%
nZole + IUI | IVF	£14,443	0.834	Dominated	£10,580 (£5,502 to £18,354)	3%	3%
IUI without OS | IVF	£15,673	0.875	Extended dominance	£10,573 (£3,954 to £18,464)	5%	1%
Gn + IUI | IVF	£16,996	0.915	£42,808	£10,442 (£5,199 to £17,517)	12%	1%

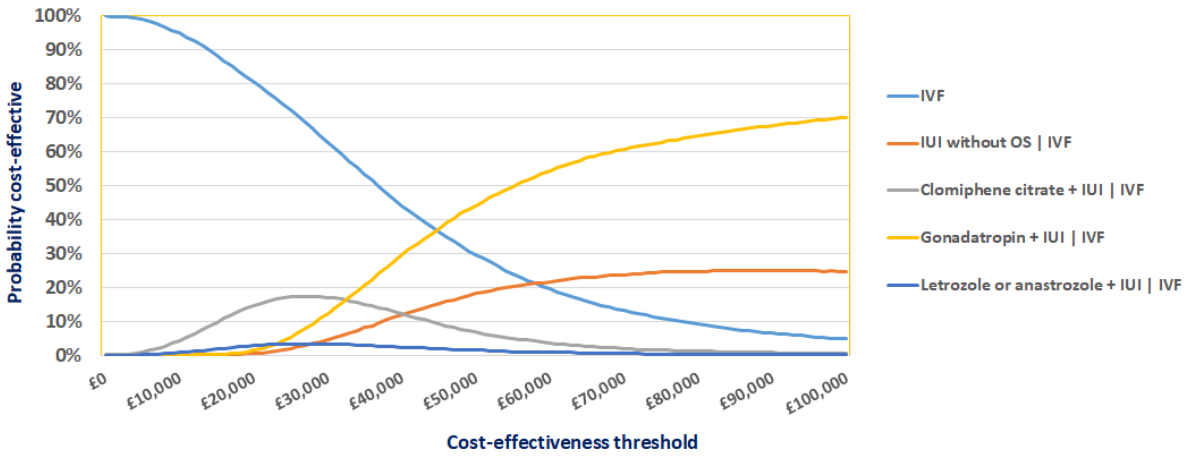
(a) Using a cost-effectiveness threshold of £30,000 per QALY
(b) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 57: PSA cost-effectiveness plane as per the base case but including singleton costs



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 58: CEAC as per the base case but including singleton costs



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

viii. As per the base case but varying treatment costs of IUI without ovarian stimulation

In the base case analysis, the unit costs of IUI without ovarian stimulation were based on the total HRG (Hospital Resource Group). This was calculated from an aggregation of day case cost data and the cost as an outpatient procedure. In this sensitivity analysis the unit costs of IUI without stimulation were based on a day case cost of £452.

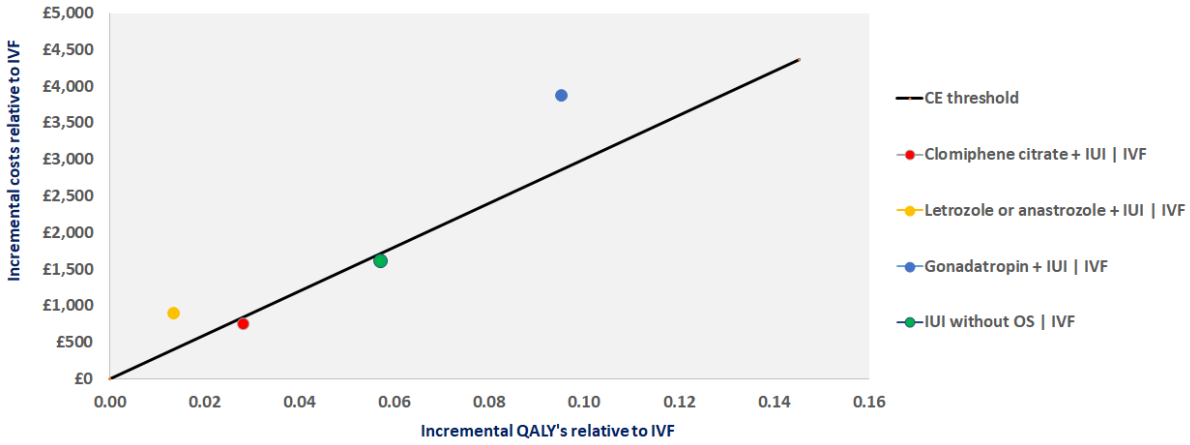
The deterministic results of this sensitivity analysis are given in Table 70 and it shows that, compared to the base case, that the relative cost-effectiveness of IUI without ovarian stimulation or IUI with clomifene citrate (an inexpensive stimulation agent) is markedly improved. Figure 59 shows that both ClomC + IUI | IVF and IUI without OS | IVF are both borderline cost-effective at a cost-effectiveness threshold of £30,000 per QALY with both strategies lying close to the cost-effectiveness threshold with ICERs of approximately £30,000 per QALY.

Table 70: Deterministic cost-effectiveness analysis as per the base case analysis but with low costs for IUI without stimulation

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,962	N/A	0.809	N/A	N/A	£14,316
ClomC + IUI | IVF	£10,696	£734	0.838	0.029	£25,962	£14,431
nZole + IUI | IVF	£10,841	N/A	0.823	N/A	Dominated	£13,849
IUI without OS | IVF	£11,572	£876	0.866	0.028	£30,353	£14,420
Gn + IUI | IVF	£13,824	£2,252	0.905	0.039	£58,922	£13,315

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 59: Cost-effectiveness plane as per the base case but with low costs for IUI without stimulation



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

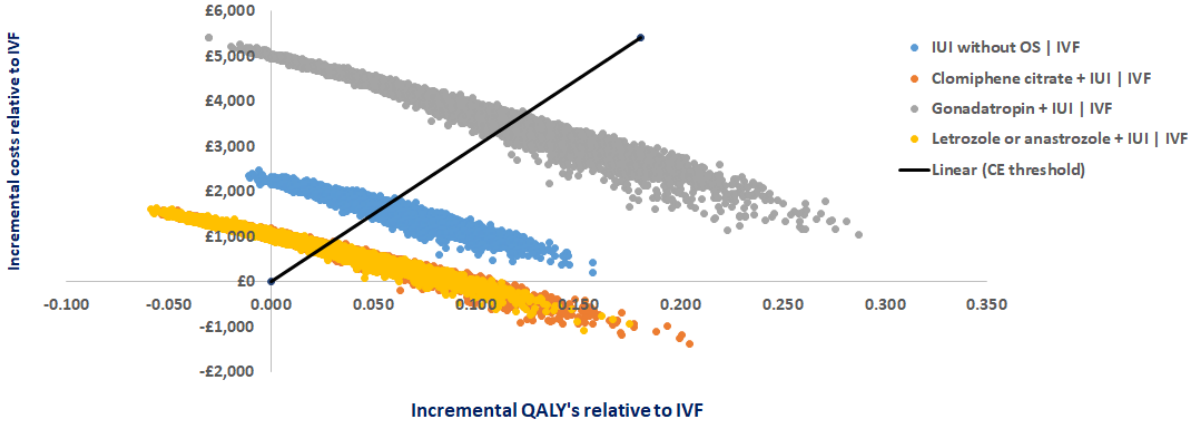
The similar cost-effectiveness of IVF, ClomC + IUI | IVF and IUI without | OS is reflected in the PSA with all strategies having similar probabilities of being the most cost-effective strategy at a cost-effectiveness threshold of £30,000 per QALY. The results of the PSA are shown in Table 71, the cost-effectiveness plane of Monte Carlo simulations in Figure 60 and the CEAC in Figure 61.

Table 71: PSA as per the base case analysis but with low costs for IUI without stimulation

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,935	0.816	N/A	£14,558 (£10,211 to £20,521)	31%	48%
ClomC + IUI | IVF	£10,619	0.848	£21,884	£14,812 (£9,168 to £21,535)	30%	34%
nZole + IUI | IVF	£10,770	0.833	Dominated	£14,216 (£8,621 to £22,944)	6%	7%
IUI without OS | IVF	£11,529	0.874	£35,173	£14,678 (£6,434 to £22,585)	27%	11%
Gn + IUI | IVF	£13,740	0.913	£55,880	£13,654 (£8,294 to £21,957)	7%	1%

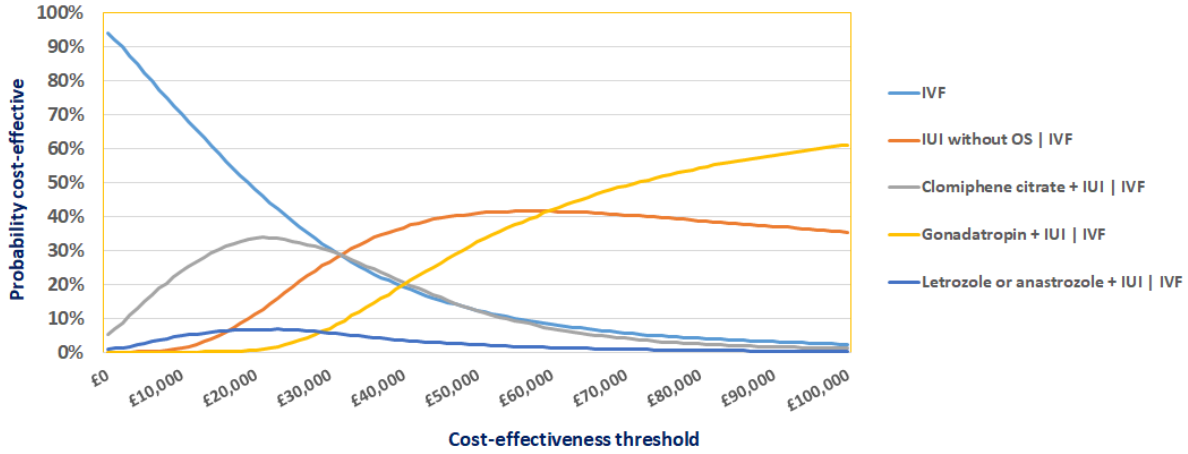
(a) Using a cost-effectiveness threshold of £30,000 per QALY
(b) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 60: PSA cost-effectiveness plane as per the base case but with low costs for IUI without stimulation



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 61: CEAC as per the base case but with low costs for IUI without stimulation



CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

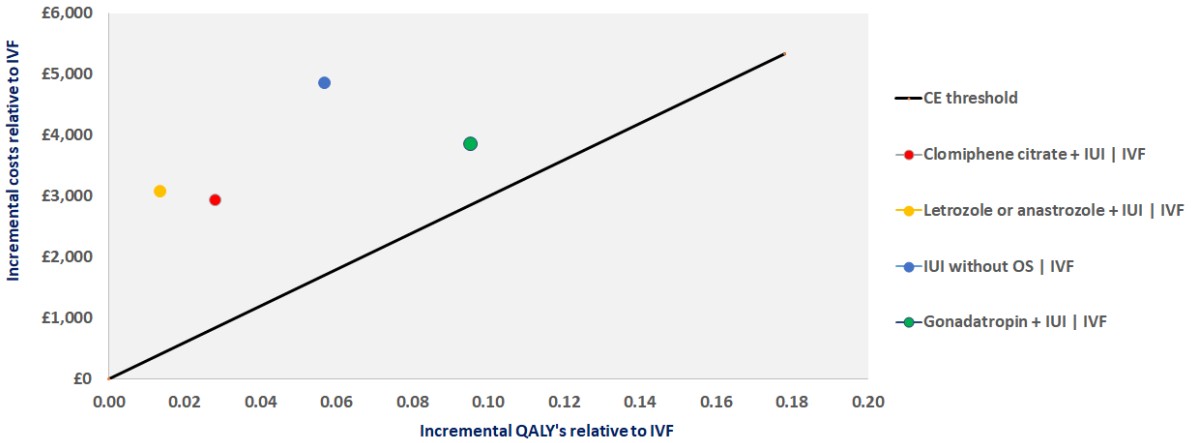
For this next sensitivity analysis the unit costs of IUI without ovarian stimulation were £1,022 to reflect NHS National Cost Collection data on outpatient procedures. The deterministic impact of this change is shown in Table 72 and the cost-effectiveness plane in Figure 62. This change has little impact on the findings as it just improves the cost-effectiveness of IVF and Gn + IUI | IVF relative to IUI without OS | IVF and IUI with low-cost ovarian stimulants (clomifene and anastrozole). As a result, as per the base, IVF remains the most cost-effective strategy with the only non-dominated option, Gn + IUI | IVF having an ICER in excess of £30,000 per QALY.

Table 72: Deterministic cost-effectiveness analysis as per the base case analysis but with high costs for IUI without stimulation

Intervention	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER	NMB
IVF	£9,962	N/A	0.809	N/A	N/A	£14,316
ClomC + IUI | IVF	£12,874	N/A	0.838	N/A	Extended dominance	£12,253
nZole + IUI | IVF	£13,032	N/A	0.823	N/A	Dominated	£11,658
Gn + IUI | IVF	£13,824	£4,030	0.905	0.096	£40,502	£13,315
IUI without OS | IVF	£14,803	N/A	0.866	N/A	Dominated	£11,189

ClomC: clomifene citrate; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; QALYs: quality-adjusted life years

Figure 62: Cost-effectiveness plane as per the base case but with high costs for IUI without stimulation



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; QALYs: quality-adjusted life years

The PSA results for the sensitivity analysis which assumes higher costs for IUI without stimulation than in the base case is presented in Table 73, a cost-effectiveness plane in Figure 63 and a CEAC in Figure 64. IVF has the highest NMB and a high probability of being the most cost-effective strategy. All IUI strategies with the exception of Gn + IUI | IVF are dominated.

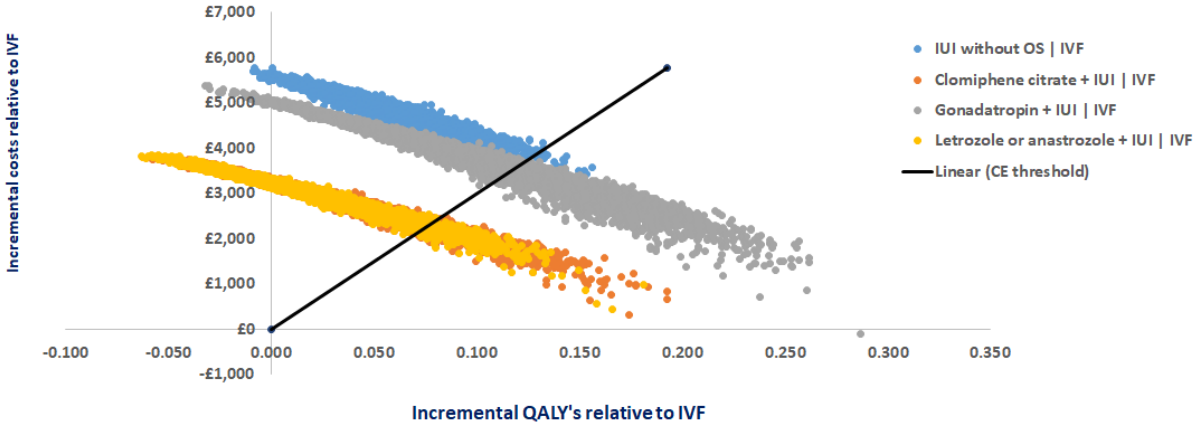
If a lower £20,000 per QALY cost-effectiveness threshold is used, then the probability of IVF being the most cost-effective strategy rises to 88%.

Table 73: PSA as per the base case analysis but with high costs for IUI without stimulation

Intervention	Mean costs	Mean QALYs	ICER	NMB (95% Cr Int)	Probability CE[a]	Probability CE[b]
IVF	£9,936	0.816	N/A	£14,545 (£10,229 to £20,544)	70%	88%
ClomC + IUI | IVF	£12,804	0.846	Extended dominance	£12,588 (£5,872 to £18,435)	0%	1%
nZole + IUI | IVF	£12,967	0.832	Dominated	£11,984 (£6,420 to £20,735)	0%	0%
Gn + IUI | IVF	£13,753	0.912	£39,814	£13,605 (£6,402 to £22,647)	30%	11%
IUI without OS | IVF	£14,761	0.873	Dominated	£11,429 (£6,016 to £19,905)	0%	0%

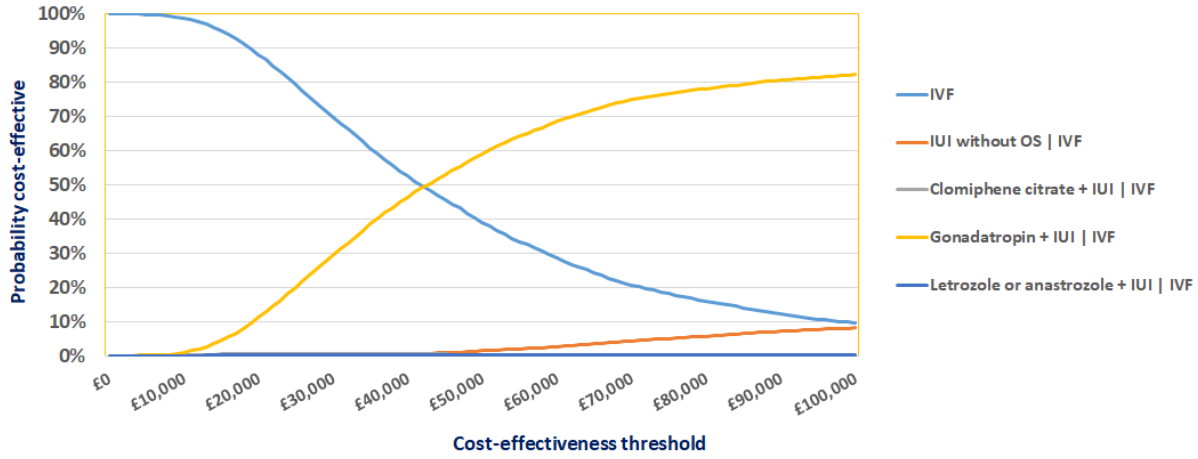
(a) Using a cost-effectiveness threshold of £30,000 per QALY
(b) Using a cost-effectiveness threshold of £20,000 per QALY
CE: cost-effectiveness; ClomC: clomifene citrate; Cr Int: credible interval; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; nZole: anastrozole/letrozole; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 63: PSA cost-effectiveness plane as per the base case but with high costs for IUI without stimulation



CE: cost-effectiveness; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years

Figure 64: CEAC as per the base case but with high costs for IUI without stimulation



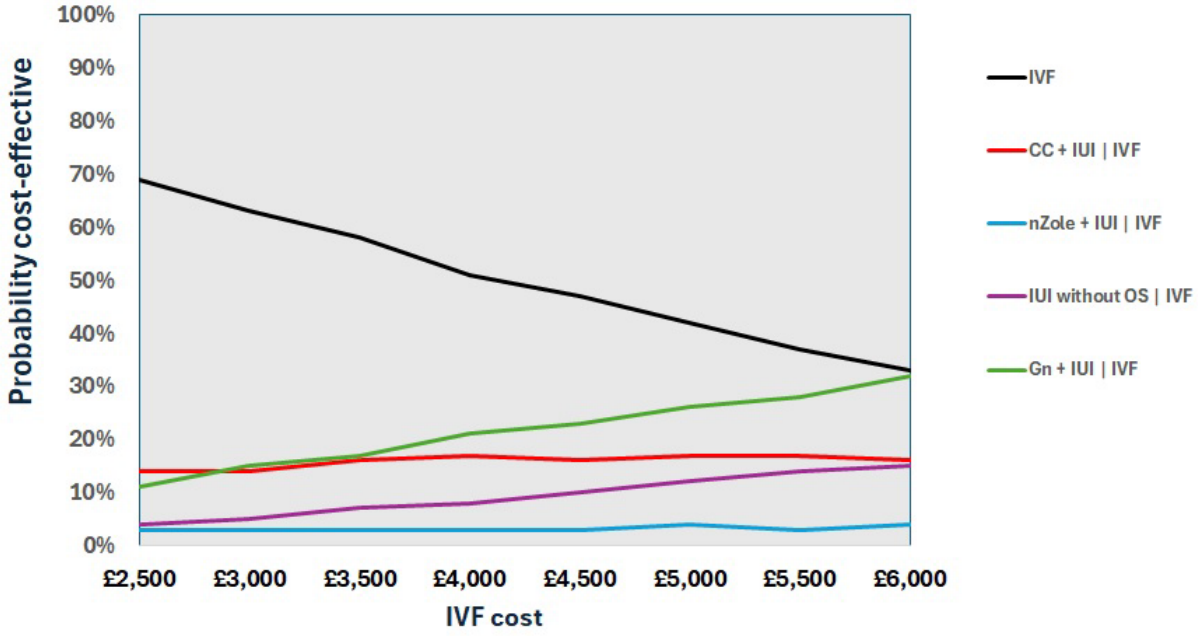
CEAC: cost-effectiveness acceptability curve; IUI: intrauterine insemination; IVF: in vitro fertilisation; OS: ovarian stimulation

ix. As per the base case but varying treatment costs of IVF

Although an NHS source was found for the base case cost of IVF treatment, the committee's understanding was that considerable uncertainty existed with respect to this estimate, although the value is not dissimilar to that reported in a recently published costing study based on Scottish NHS fertility centres (Venson, 2023). Therefore, a sensitivity analysis was undertaken to assess the impact of varying the treatment cost of IVF between £2,500 and £6,000. For these analyses the cost of an IVF cycle cancelled post-harvest was amended also in cases where the IVF treatment cost was lower than the base case cost of an IVF cycle cancelled post-harvest. In those cases, the cost of an IVF cycle cancelled post-harvest was assumed to be the same as the lower value IVF treatment cost.

Figure 65 shows how the probability of IVF being cost-effective declines with increasing IVF cost. Whilst IVF continues to have the highest probability of being cost-effective up to an IVF treatment cost of £6,000, the uncertainty with respect to the optimal strategy increases markedly with increasing IVF treatment cost.

Figure 65: Graph to show the impact of a sensitivity analysis varying the cost of IVF treatment on the probability that different strategies are cost-effective



CC: clomifene citrate; Gn: gonadotropin; IUI: intrauterine insemination; IVF: in vitro fertilisation; nZole: anastrozole/letrozole; OS: ovarian stimulation

With the exception of the sensitivity analysis which assumed a lower treatment cost for IUI without stimulation, all analyses suggested that either IVF or Gn + IUI | IVF was the most cost-effective treatment at a cost-effectiveness threshold of £30,000 per QALY. Table 74 below provides a summary comparison of these 2 strategies across all the analyses presented in this report.

Table 74: Summary of cost-effectiveness results for IVF and Gn + IUI | IVF

Analysis	IVF		Gn + IUI | IVF		
	NMB	P (CE)[a]	NMB	ICER	P (CE)[a]
Base case analysis	**£14,616**	**55%**	£13,370	£39,124	18%
Higher baseline births [b]	£17,622	17%	**£18,738**	**£28,806**	**37%**
Depletion of susceptibles [c]	**£13,763**	**65%**	£12,561	£43,675	16%
Higher baseline births plus depletion of susceptibles [b,c]	£16,841	24%	**£17,494**	**£28,454**	**37%**
Time horizon: 36 months	**£8,717**	**43%**	£8,476	£32,033	29%
Time horizon: maximum treatment duration	£4,781	**35%**	**£5,046**	**£28,048**	37%

Analysis	IVF		Gn + IUI | IVF		
	NMB	P (CE)[a]	NMB	ICER	P (CE)[a]
Higher health state utility gain from live birth	£39,187	16%	**£41,211**	**£19,576**	**56%**
Low age starting treatment	**£18,731**	**57%**	£17,492	£39,947	20%
High age starting treatment	**-£1,911**	**93%**	-£4,938	£78,187	2%
Including singleton costs	**£11,683**	**63%**	£10,442	£42,808	12%
Low treatment cost of IUI without OS	**£14,558**	**31%**	£13,654	£55,850 [d]	7%
High treatment cost of IUI without OS	**£15,545**	**70%**	£13,605	£39,814	30%
Low cost of IVF	**£17,544**	**69%**	£16,081	£45,028	11%
High cost of IVF	£8,882	**33%**	**£9,127**	£30,751 [e]	32%

(a) Probability cost-effective at a cost-effectiveness threshold of £30,000 per QALY
(b) Baseline live births based on expectant management are in Bhattacharya 2008
(c) Assumes 5% of population who did not have a live birth after first line treatment are genuinely infertile
(d) Calculated relative to IUI without OS | IVF
(e) Calculated relative to ClomC + IUI | IVF
CE: cost-effectiveness; Gn: gonadotropin; ICER: incremental cost-effectiveness ratio; IUI: intrauterine insemination; IVF: in vitro fertilisation; N/A: not applicable; NMB: net monetary benefit; OS: ovarian stimulation; P (CE): probability cost-effective

Discussions

In all the analyses presented, the IVF strategy (IVF alone followed by possibility of spontaneous conception leading to live birth by expectant management) is the cheapest treatment strategy despite IVF being the most expensive individual treatment option. Primarily this is because IUI effectiveness, when provided 1st line, is not sufficient to prevent a significant proportion of the population going on to receive 2nd line IVF. The combined treatment cost of strategies which utilise less expensive IUI followed by IVF where 1st line treatment has not resulted in live birth are more expensive than IVF alone because the additional costs of 2nd line IVF exceed any saving from the use of IUI treatment 1st line.

In nearly all analyses, the IVF strategy was also the least effective in terms of cumulative live births and QALYs. If IVF is assumed to be equally effective 2nd line, then this lower IVF strategy effectiveness is an inevitable consequence of offering an additional treatment option (IUI) prior to IVF. However, even where depletion of susceptibles were taken into account (see for example, Table 59) the IVF strategy usually remained least effective with the benefit of an additional treatment (IUI) not being completely offset by lower effectiveness of IVF when offered as a 2nd line treatment. However, when the depletion of susceptible was assumed to be relatively large (for example, proxied by assuming that 25% who did not have a live birth with 1st line treatment were genuinely infertile) then IVF dominated ClomC + IUI |

IVF and nZole + IUI | IVF, producing a higher cumulative live birth rate at a lower cost. Nevertheless, the IUI without OS | IVF and Gn + IUI | IVF strategies continued to produce the highest live birth rates even with this assumption about reduced IVF effectiveness 2nd line.

ClomC + IUI | IVF always dominates nZole + IUI | IVF reflecting its slightly cheaper treatment cost (Table 48) and greater relative treatment effect (Table 45) which also leads to fewer cycles and 2nd line treatment. However, apart from the sensitivity analysis where a lower cost for IUI without ovarian stimulation was assumed, Gn + IUI | IVF had extended dominance over ClomC + IUI | IVF and IUI without OS | IVF. Therefore, apart from in that sensitivity analysis, either IVF or Gn + IUI | IVF were the most cost-effective strategy.

In the sensitivity analysis where a higher cost is assumed for IUI without OS, then Gn + IUI | IVF dominates IUI without OS | IVF because, although Gn + IUI | IVF remains the more expensive treatment, these are more than offset by the higher cumulative birth rates leading to a lower number of cycles and treatments.

As shown in Table 53, twin and OHSS costs contributed a very small amount to the overall costs of any of the strategies. IVF strategy has the lowest twin costs which partly reflects that a lower risk of twin birth is assumed for IVF than IUI (Table 46) but more importantly twin costs are a function of the cumulative live birth rate. OHSS costs are a reflection of the risk of OHSS occurring and the number of cycles that are offered as part of a strategy (Table 41 and Table 47).

Whilst there is considerable uncertainty with respect to the health state utility loss from OHSS, it makes a negligible difference to the overall QALY gain from any particular strategy and is not an important driver of model results. This is a consequence of the relatively low probability of moderate or severe OHSS occurring and its short duration, meaning that any QALY loss is limited even when it occurs.

Increasing the baseline live birth rate, as shown in the sensitivity analysis using Bhattacharya 2008 data, has the consequence of increasing the absolute treatment effect and therefore the strategies that give relatively higher cumulative birth rates become relatively more cost-effective under such assumptions and Gn + IUI | IVF is more likely to be a cost-effective alternative to IVF alone in these scenarios. Conversely, accounting for a depletion of susceptible effect tends to make IVF more cost-effective relative to the alternatives as its impact is to reduce the absolute treatment benefit of 2nd line IVF compared to the base case analysis. The greater the depletion of susceptible effect (see Figure 41) then the more likely IVF is to be cost-effective. A depletion of susceptible effect could also occur in subsequent cycles in a 1st line treatment, but this will be reflected in the estimates of cumulative live birth rates in the studies that contributed to the NMA.

Shorter time horizons tend to improve the cost-effectiveness of Gn + IUI | IVF relative to IVF. This is because the shorter time horizon means there is less time for expectant management to reduce the absolute differences in cumulative live birth rates in those strategies which have a smaller cumulative live birth rate following the completion of all available treatment cycles.

The use of QALYs is problematic in the assessment of fertility treatments (Keller 2022) and considerable uncertainty exists with regard to how a live birth should be valued, not least because the negative impact of infertility may impact on broader measures of well-being than health-related quality of life. This is why we gave greater focus to results using a £30,000 per QALY cost-effectiveness threshold than the more conservative threshold of £20,000 per QALY. This uncertainty is an important limitation in interpreting the results of this evaluation as sensitivity analysis indicated assumptions about the precise value of health state utility gain attributable to a live birth had a large bearing on the cost-effectiveness conclusions

generated by the model (see Figure 54). The model indicated that for a health state utility gain of less than 0.10 per live birth then IVF had the highest probability of being cost-effective but above that amount Gn + IUI | IVF was most likely to be cost-effective. This is because increasing the health state utility leads to increased QALYs and therefore NMB, which has the largest absolute impact on strategies with the highest cumulative live birth rates.

Age at starting treatment impacts on the baseline live birth rate with the probability of spontaneous conception leading to live birth declining with increasing age. Thus, when a relative treatment effect is applied to this declining baseline probability, the absolute treatment benefit is reduced leading to lower QALYs and higher "downstream" costs, arising from more unsuccessful cycles and treatment. This means that the higher costs are associated with more effective treatment are less likely to represent value for money.

The sensitivity analysis which considered the cost of singleton as well as multiple births made relatively little difference to the results obtained in the base case. This is because the costs increase across all strategies and therefore it mostly cancels out although the bigger impact is on the most effective strategies and therefore, as there is no QALY change, then there IVF does relatively become slightly more cost-effective.

Treatment costs are important drivers of the model and if IUI without OS costs are over-estimated in the model then ClomC + IUI and IUI without OS would become relatively cheaper than Gn + IUI with a concomitant impact on their relative cost-effectiveness. The certainty with which IVF can be considered cost-effective decreased markedly with increasing costs (Figure 65) although even at almost double the base case estimate, it still has the highest probability of being cost-effective.

Finally, it is important to note other limitations in the analysis when interpreting the results. Limitations in the clinical data and NMA will be replicated as limitations in the HE model. For example, the guideline committee believe that IVF live birth rates continue to improve in which case IVF studies in the NMA may not accurately reflect what can be expected in current practice. Studies in the NMA did not always offer the same number of treatment cycles and therefore it was hoped that interventions could be grouped into categories which reflected the number of cycles as it was expected a priori that those interventions offering more cycles would be likely to have higher cumulative live birth rates. However, this approach led to a disconnected network and therefore had to be abandoned for an approach that grouped studies using a more basic treatment classification where cycles may have varied both within and between groups.

Conclusions

Subject to a number of limitations this analysis provides strong evidence that IVF as a 1st line treatment is cost-effective. When a £20,000 cost per QALY cost-effectiveness threshold was used then IVF always emerged as the most cost-effective strategy and under many of the scenarios presented it was also the most cost-effective if a £30,000 cost per QALY threshold was used. Sensitivity analysis indicated that if there was a depletion of susceptible effect, then that would reinforce the conclusion that IVF was the most cost-effective strategy.

However, given the uncertainty around baseline spontaneous conception but especially the valuation of the gains from a live birth, the committee thought there was sufficient cost-effectiveness evidence to support a weaker recommendation to offer gonadotropin plus IUI as a 1st line treatment followed by IVF if unsuccessful. This was because a number of sensitivity analyses suggested that Gn + IUI | IVF could be cost-effective at the higher cost-effectiveness threshold of £30,000 per QALY if certain uncertain parameter values in the model were changed.

The committee did not think the health economic evidence supported recommendations for IUI without ovarian stimulation or to use either clomifene, letrozole or anastrozole as stimulation agents for IUI.

References

Bahadur 2020

Bahadur G, Homburg R, Bosmans JE, et al. Observational retrospective study of UK national success, risks and costs for 319,105 IVF/ICSI and 30,669 IUI treatment cycles. BMJ Open 16;10(3), 2020

Devlin 2018

Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Economics. 27(1):7-22, 2018

Gleicher 2009

Gleicher N, Barad D. Twin pregnancy, contrary to consensus, is a desirable outcome in infertility. Fertility and Sterility. 91(6):2426-31, 2009

Heller 2022

Keller E, Chambers GM. Valuing infertility treatment: Why QALYs are inadequate, and an alternative approach to cost-effectiveness thresholds. Frontiers in Medical Technology. 4:1053719, 2022

Koutsouki 2023

Koutsouki E. Guidelines on unexplained fertility. European Medical Journal Reproductive Health. 9[1]:23-26, 2023

Practice Committee of the American Society for Reproductive Medicine.

Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertility and Sterility. 113(2):305-322, 2020

Scotland 2011

Scotland GS, McLernon D, Kurinczuk JJ, McNamee P, Harrild K, Lyall H, Rajkhowa M, Hamilton M, Bhattacharya S. Minimising twins in in vitro fertilisation: a modelling study assessing the costs, consequences and cost-utility of elective single versus double embryo transfer over a 20-year time horizon. British Journal of Obstetrics & Gynaecology 118(9):1073-83, 2011

Skedgel 2023

Skedgel C, Cubi-Molla P, Mott D, Gameiro S, Boivin J, Al-Janabi H, Brazier J, Markert M, Andersson FL, Jofre-Bonet M. Unmet Parenthood Goals, Health-Related Quality of Life and Apparent Irrationality: Understanding the Value of Treatments for Infertility. Pharmacoeconomics Open. 7(3):337-344, 2023

Sood 2020

Sood, A., Goel, A., Boda, S., & Mathur, R. Prediction of significant OHSS by ovarian reserve and ovarian response – implications for elective freeze-all strategy. Human Fertility, 25(2), 390–396, 2029

van Eekelen 2017

van Eekelen R, Scholten I, Tjon-Kon-Fat RI, van der Steeg JW, Steures P, Hompes P, van Wely M, van der Veen F, Mol BW, Eijkemans MJ, Te Velde ER, van Geloven N. Natural conception: repeated predictions over time. Human Reproduction. 32(2):346-353, 2017

Quality of life references

The following 15 studies ordered for full text review met the applicability criteria for the QoL life sift and were therefore screened comprehensively for inclusion:

Agostini 2017

Agostini F, Monti F, Andrei F, Paterlini M, Palomba S, La Sala GB. Assisted reproductive technology treatments and quality of life: a longitudinal study among subfertile women and men. J Assist Reprod Genet. 2017 Oct;34(10):1307-1315. doi: 10.1007/s10815-017-1000-9. Epub 2017 Jul 21. PMID: 28733802; PMCID: PMC5633563.

Ahmadi 2014

Ahmadi SE, Montazeri A, Mozafari R, Azari A, Nateghi MR, Ashrafi M. Health-Related Quality of Life and Primi-Gravid: A Comparative Study of Natural Conception and Conception by Assisted Reproduction Technologies (ARTs). Int J Fertil Steril. 2014 Jul;8(2):167-74. Epub 2014 Jul 8. PMID: 25083182; PMCID: PMC4107691.

Ashraf 2015

Ashraf DM, Ali D, Azadeh DM. Effect of infertility on the quality of life, a cross- sectional study. J Clin Diagn Res. 2014 Oct;8(10):OC13-5. doi: 10.7860/JCDR/2014/8481.5063. Epub 2014 Oct 20. Erratum in: J Clin Diagn Res. 2015 Aug;9(8):ZZ02. doi: 10.7860/JCDR/2015/8481.6536. PMID: 25478412; PMCID: PMC4253230.

Botha 2018

Botha W, Donnolley N, Shanahan M, Norman RJ, Chambers GM. Societal preferences for fertility treatment in Australia: a stated preference discrete choice experiment. J Med Econ. 2019 Jan;22(1):95-107. doi: 10.1080/13696998.2018.1549055. Epub 2018 Dec 6. PMID: 30431385.

Fenwick 2023

Fenwick E, Eze A, D'Hooghe T, Pandey S, Chaudhari VS, Ostawal A, Luyten J, Harty G. The value of treatment for infertility: A systematic literature review of willingness-to-pay thresholds and approaches for determining the cost effectiveness of fertility therapies. Best Pract Res Clin Obstet Gynaecol. 2023 Jul;89:102340. doi: 10.1016/j.bpobgyn.2023.102340. Epub 2023 Apr 18. PMID: 37290265.

El Kissi 2014

El Kissi Y, Amamou B, Hidar S, Ayoubi Idrissi K, Khairi H, Ali BB. Quality of life of infertile Tunisian couples and differences according to gender. Int J Gynaecol Obstet. 2014 May;125(2):134-7. doi: 10.1016/j.ijgo.2013.10.027. Epub 2014 Feb 4. PMID: 24568955.

Gambadauro 2023

Gambadauro, P., Bränn, E. & Hadlaczky, G. Acceptance and willingness-to-pay for oocyte cryopreservation in medical versus age-related fertility preservation scenarios among Swedish female university students. Sci Rep 13, 5325 (2023).

Kato 2021

Kato T, Sampei M, Saito K, Morisaki N, Urayama KY. Author Correction: Depressive symptoms, anxiety, and quality of life of Japanese women at initiation of ART treatment. Sci Rep. 2021 Nov 17;11(1):22793. doi: 10.1038/s41598-021-02389-7. Erratum for: Sci Rep. 2021 Apr 6;11(1):7538. doi: 10.1038/s41598-021-87057-6. PMID: 34789852; PMCID: PMC8599490.

Keller 2023

Keller E, Botha W, Chambers GM. What Features of Fertility Treatment do Patients Value? Price Elasticity and Willingness-to-Pay Values from a Discrete Choice Experiment. Appl Health Econ Health Policy. 2023 Jan;21(1):91-107. doi: 10.1007/s40258-022-00764-7. Epub 2022 Sep 29. PMID: 36171511; PMCID: PMC9834167.

Krol 2019

Krol M, Nap A, Michels R, Veraart C, Goossens L. Health state utilities for infertility and subfertility. Reprod Health. 2019 May 3;16(1):47. doi: 10.1186/s12978-019-0706-9. PMID: 31053144; PMCID: PMC6499998.

Milman 2017

Milman LW, Senapati S, Sammel MD, Cameron KD, Gracia C. Assessing reproductive choices of women and the likelihood of oocyte cryopreservation in the era of elective oocyte freezing. Fertil Steril. 2017 May;107(5):1214-1222.e3. doi: 10.1016/j.fertnstert.2017.03.010. PMID: 28476182; PMCID: PMC5523852.

Ragni 2005

Ragni G, Mosconi P, Baldini MP, Somigliana E, Vegetti W, Caliari I, Nicolosi AE. Health-related quality of life and need for IVF in 1000 Italian infertile couples. Hum Reprod. 2005 May;20(5):1286-91. doi: 10.1093/humrep/deh788. Epub 2005 Feb 3. PMID: 15695309.

Scotland 2011

Scotland GS, McLernon D, Kurinczuk JJ, McNamee P, Harrild K, Lyall H, Rajkhowa M, Hamilton M, Bhattacharya S. Minimising twins in in vitro fertilisation: a modelling study assessing the costs, consequences and cost-utility of elective single versus double embryo transfer over a 20-year time horizon. British Journal of Obstetrics & Gynaecology 118(9):1073-83, 2011

Sezgin 2016

Sezgin H, Hocaoglu C, Guvendag-Guven ES. Disability, psychiatric symptoms, and quality of life in infertile women: a cross-sectional study in Turkey. Shanghai Arch Psychiatry. 2016 Apr

25;28(2):86-94. doi: 10.11919/j.issn.1002-0829.216014. PMID: 27605864; PMCID: PMC5004092.

Skedgel 2021

Skedgel C, Ralphs E, Finn E, Whitty JA, Markert M, Samuelsen C. Is the public supportive and willing to pay for a national assistive reproductive therapies programme? Results from a multicountry survey. BMJ Open. 2021 Mar 10;11(3):e044986. doi: 10.1136/bmjopen-2020-044986. PMID: 33692187; PMCID: PMC7949370.

The remaining 18 studies listed below were rated as not applicable after full text review:

Bagade 2022

Bagade T, Thapaliya K, Breuer E, Kamath R, Li Z, Sullivan E, Majeed T. Investigating the association between infertility and psychological distress using Australian Longitudinal Study on Women's Health (ALSWH). Sci Rep. 2022 Jun 25;12(1):10808. doi: 10.1038/s41598-022-15064-2. PMID: 35752691; PMCID: PMC9233676.

Carter 2011

Carter J, Applegarth L, Josephs L, Grill E, Baser RE, Rosenwaks Z. A cross-sectional cohort study of infertile women awaiting oocyte donation: the emotional, sexual, and quality-of-life impact. Fertil Steril. 2011 Feb;95(2):711-6.e1. doi: 10.1016/j.fertnstert.2010.10.004. Epub 2010 Nov 5. PMID: 21055740.

Collins 2017

Collins SC, Xu X, Mak W. Cost-effectiveness of preimplantation genetic screening for women older than 37 undergoing in vitro fertilization. J Assist Reprod Genet. 2017 Nov;34(11):1515-1522. doi: 10.1007/s10815-017-1001-8. Epub 2017 Jul 27. PMID: 28748493; PMCID: PMC5699982.

Cornelissee 2022

Cornelisse S, Vos MS, Groenewoud H, Mastenbroek S, Ramos L, Braat DDM, Stalmeier PFM, Fleischer K. Women's preferences concerning IVF treatment: a discrete choice experiment with particular focus on embryo transfer policy. Hum Reprod Open. 2022 Jul 13;2022(3):hoac030. doi: 10.1093/hropen/hoac030. PMID: 35928049; PMCID: PMC9345060.

Goldhaber-Fiebert 2015

Goldhaber-Fiebert JD, Brandeau ML. Evaluating Cost-effectiveness of Interventions That Affect Fertility and Childbearing: How Health Effects Are Measured Matters. Med Decis Making. 2015 Oct;35(7):818-46. doi: 10.1177/0272989X15583845. Epub 2015 Apr 29. PMID: 25926281; PMCID: PMC4418217.

Gonen 2017

Gonen, L.D. The willingness to pay for in vitro fertilization-related information and its attributes: a cross-sectional study in Israel. *Health Serv Outcomes Res Method* **17**, 56–83 (2017).

Jin 2023

Jin C, Tooth LR, Xu X, Mishra GD. Do mothers or females without children have better health-related quality of life across their reproductive years? Qual Life Res. 2023 May;32(5):1481-1491. doi: 10.1007/s11136-022-03338-1. Epub 2023 Jan 4. PMID: 36598639.

Keller 2023

Keller E, Botha W, Chambers GM. Does *in vitro* fertilization (IVF) treatment provide good value for money? A cost-benefit analysis. Front Glob Womens Health. 2023 Mar 1;4:971553. doi: 10.3389/fgwh.2023.971553. PMID: 36937042; PMCID: PMC10014591.

Keller 2022

Keller E, Chambers GM. Valuing infertility treatment: Why QALYs are inadequate, and an alternative approach to cost-effectiveness thresholds. Front Med Technol. 2022 Dec 23;4:1053719. doi: 10.3389/fmedt.2022.1053719. PMID: 36619344; PMCID: PMC9822722.

Le 2018

Le KD, Vuong LN, Ho TM, Dang VQ, Pham TD, Pham CT, Norman RJ, Mol BWJ. A cost-effectiveness analysis of freeze-only or fresh embryo transfer in IVF of non-PCOS women. Hum Reprod. 2018 Oct 1;33(10):1907-1914. doi: 10.1093/humrep/dey253. PMID: 30239784.

Lund 2009

Lund R, Sejbaek CS, Christensen U, Schmidt L. The impact of social relations on the incidence of severe depressive symptoms among infertile women and men. Hum Reprod. 2009 Nov;24(11):2810-20. doi: 10.1093/humrep/dep257. Epub 2009 Jul 22. PMID: 19625314.

Peterson 2014

Peterson BD, Sejbaek CS, Pirritano M, Schmidt L. Are severe depressive symptoms associated with infertility-related distress in individuals and their partners? Hum Reprod. 2014 Jan;29(1):76-82. doi: 10.1093/humrep/det412. Epub 2013 Nov 19. PMID: 24256990.

Polyakov 2022

Polyakov A, Gyngel C, Savulescu J. Modelling futility in the setting of fertility treatment. Hum Reprod. 2022 May 3;37(5):877-883. doi: 10.1093/humrep/deac051. PMID: 35298646; PMCID: PMC9071221.

Postmus 2014

Postmus D, Tervonen T, van Valkenhoef G, Hillege HL, Buskens E. A multi-criteria decision analysis perspective on the health economic evaluation of medical interventions. Eur J Health Econ. 2014 Sep;15(7):709-16. doi: 10.1007/s10198-013-0517-9. Epub 2013 Jul 11. PMID: 23843123.

Settumba 2019

Settumba SN, Shanahan M, Botha W, Ramli MZ, Chambers GM. Reliability and Validity of the Contingent Valuation Method for Estimating Willingness to Pay: A Case of In Vitro Fertilisation. Appl Health Econ Health Policy. 2019 Feb;17(1):103-110. doi: 10.1007/s40258-018-0433-3. PMID: 30315488.

Spigel 2013

Spiegel, U., Gonen, L.D. & Templeman, J. Economic implications of in vitro fertilization using willingness to pay. J Public Health 21, 535–557 (2013).

Teskereci 2013

Teskereci G, Oncel S. Effect of lifestyle on quality of life of couples receiving infertility treatment. J Sex Marital Ther. 2013;39(6):476-92. doi: 10.1080/0092623X.2012.665817. Epub 2013 Apr 30. PMID: 23631703.

van Heesch 2016

van Heesch MM, van Asselt AD, Evers JL, van der Hoeven MA et al. Cost-effectiveness of embryo transfer strategies: a decision analytic model using long-term costs and consequences of singletons and multiples born as a consequence of IVF. Hum Reprod. 2016 Nov;31(11):2527-2540. doi: 10.1093/humrep/dew229. Epub 2016 Oct 6. PMID: 27907897.

Appendix J Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Excluded effectiveness studies

Table 75: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Abuzeid, O M, Deanna, J, Abdelaziz, A et al. (2017) The impact of single versus double blastocyst transfer on pregnancy outcomes: A prospective, randomized control trial. Facts, views & vision in ObGyn 9(4): 195-206	- Intervention not in PICO *ICSI*
Anonymous (2009) Intrauterine insemination. Human reproduction update 15(3): 265-77	- Systematic review, included studies checked for relevance
Asgharnia, Maryam, Mehrafza, Marzieh, Raoufi, Azadeh et al. (2022) The efficiency of low-dose letrozole plus clomiphene citrate for ovulation induction in intrauterine insemination cycles: A randomized clinical trial. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 159(1): 182-187	- Population not in PICO *<80% of participants had unexplained infertility or mild male factor infertility*
Attia, A.M.; Al-Inany, H.G.; Proctor, M.L. (2007) Gonadotrophins for idiopathic male factor subfertility: A Cochrane systematic review. Middle East Fertility Society Journal 12(2): 77-85	- Systematic review, included studies checked for relevance

Study	Code [Reason]
Attia, Abdelhamid M; Abou-Setta, Ahmed M; Al-Inany, Hesham G (2013) Gonadotrophins for idiopathic male factor subfertility. The Cochrane database of systematic reviews: cd005071	- Systematic review, included studies checked for relevance
Ayaz, Reyhan; Asoglu, Mehmet Resit; Ayas, Selcuk (2018) Use of clomiphene citrate alone, urinary follicle-stimulating hormone alone, or both combined sequentially in patients with unexplained subfertility undergoing intrauterine insemination: A randomized trial. Turkish journal of obstetrics and gynecology 15(4): 243-248	- Study design not in PICO *Quasi-RCT*
Ayeleke, R.O., Asseler, J.D., Cohlen, B.J. et al. (2020) Intra-uterine insemination for unexplained subfertility. Cochrane Database of Systematic Reviews 2020(3): cd001838	- Systematic review, included studies checked for relevance
Ayeleke, Reuben Olugbenga, Asseler, Joyce Danielle, Cohlen, Ben J et al. (2020) Intra-uterine insemination for unexplained subfertility. The Cochrane database of systematic reviews 3: cd001838	- Duplicate reference
Azmoodeh, Azra, Pejman Manesh, Mansoureh, Akbari Asbagh, Firouzeh et al. (2015) Effects of Letrozole-HMG and Clomiphene-HMG on Incidence of Luteinized Unruptured Follicle Syndrome in Infertile Women Undergoing Induction Ovulation and Intrauterine Insemination: A Randomised Trial. Global journal of health science 8(4): 244-52	- Population not in PICO *Only 41% of participants had unexplained infertility, and data not reported separately for those with unexplained infertility*
Badawy, A; Elnashar, A; Totongy, M (2010) Clomiphene citrate or aromatase inhibitors combined with gonadotropins for superovulation in women undergoing intrauterine insemination: a prospective randomised trial. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 30(6): 617-21	- Retracted article
Badawy, Ahmed, Shokeir, Tarek, Allam, Abdel Fattah et al. (2009) Pregnancy outcome after ovulation induction with aromatase inhibitors or clomiphene citrate in unexplained infertility. Acta obstetricia et gynecologica Scandinavica 88(2): 187-91	- Expression of concern *Editorial note about an ongoing investigation in response to concerns raised regarding the authenticity of the data presented within this article*
Barroso, Gerardo, Menocal, Gerardo, Felix, Hector et al. (2006) Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial. Fertility and sterility 86(5): 1428-31	- Study design not in PICO *Quasi-RCT*
Bastu, Ercan, Buyru, Faruk, Ozsurmeli, Mehmet et al. (2016) A randomized, single-blind, prospective	- Comparison not in PICO

Study	Code [Reason]
trial comparing three different gonadotropin doses with or without addition of letrozole during ovulation stimulation in patients with poor ovarian response. European journal of obstetrics, gynecology, and reproductive biology 203: 30-4	*Comparison between different ovarian stimulation agents for IVF*
Baysoy, Aynur, Serdaroglu, Hasan, Jamal, Hashim et al. (2006) Letrozole versus human menopausal gonadotrophin in women undergoing intrauterine insemination. Reproductive biomedicine online 13(2): 208-12	- Not first-line treatment *Not first-line treatment - all participants had previously undergone at least 1 cycle of ovulation induction with timed intercourse*
Bedaiwy, Mohamed A, Forman, Rachel, Mousa, Noha A et al. (2006) Cost-effectiveness of aromatase inhibitor co-treatment for controlled ovarian stimulation. Human reproduction (Oxford, England) 21(11): 2838-44	- Study design not in PICO *Clinical results not from a RCT*
Bedaiwy, Mohamed A, Mousa, Noha A, Esfandiari, Navid et al. (2007) Follicular phase dynamics with combined aromatase inhibitor and follicle stimulating hormone treatment. The Journal of clinical endocrinology and metabolism 92(3): 825-33	- Study design not in PICO *Not a RCT*
Behre, HM (2003) Clinical efficacy of recombinant human chorionic gonadotropin for the treatment of infertile women. Journal fur fertilitat und reproduktion 13(2): 33-35	- Study not reported in English
Berker, Bulent, Kahraman, Korhan, Taskin, Salih et al. (2011) Recombinant FSH versus clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing intrauterine insemination: a randomized trial. Archives of gynecology and obstetrics 284(6): 1561-6	- Data cannot be extracted *Only 1 cycle included for each participant but unclear how they selected which cycle to include and the number of previous OH/IUI cycles suggests they did not just select the first cycle*
Cantineau, A E P; Cohlen, B J; Heineman, M J (2007) Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. The Cochrane database of systematic reviews: cd005356	- Systematic review, included studies checked for relevance
Cantineau, Astrid Ep; Rutten, Anouk Gh; Cohlen, Ben J (2021) Agents for ovarian stimulation for intrauterine insemination (IUI) in ovulatory women with infertility. The Cochrane database of systematic reviews 11: cd005356	- Systematic review, included studies checked for relevance
Chaudhury, Kalyansree, Chaudhury, Sudeshna, Khastgir, Gautam et al. (2013) An effective alternative to only gonadotrophin for controlled ovarian stimulation in unexplained infertility patients undergoing intra-uterine insemination: a clinical trial. Journal of the Indian Medical Association 111(9): 589-594	- Study design not in PICO *Quasi-RCT*

Study	Code [Reason]
Costello, Michael F (2004) Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination. The Australian & New Zealand journal of obstetrics & gynaecology 44(2): 93-102	- Systematic review, included studies checked for relevance
Currie, C.J. and Wechowski, J.G. (2006) Randomized single versus double embryo transfer studies: Obstetric and paediatric outcome and a cost-effectiveness analysis [3]. Human Reproduction 21(7): 1939-1940	- Study design not in PICO *Commentary*
Custers, I, Hompes, P, Broekmans, F et al. (2009) IVF with elective single embryo transfer versus IUI-COH in couples with unexplained subfertility and a poor prognosis: a multicentre RCT. Human reproduction. European society of human reproduction and embryology, ESHRE 25th annual meeting amsterdam 28th june to 1st july 2009. 24suppl1: i76 O-188 Oral	- Conference abstract *Data cannot be extracted from elsewhere (for instance, from an existing systematic review)*
Custers, Inge M, van Rumste, Minouche M E, van der Steeg, Jan Willem et al. (2012) Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. Human reproduction (Oxford, England) 27(2): 444-50	- Not first-line treatment *Further-line fertility treatments (at 6 months after randomisation, expectant management group had IVF or IUI and IUI with ovarian stimulation group had IUI alone or IVF)*
Danhof, N A, van Eekelen, R, Repping, S et al. (2020) Endometrial thickness as a biomarker for ongoing pregnancy in IUI for unexplained subfertility: a secondary analysis. Human reproduction open 2020(1): hoz024	- Study design not in PICO *Secondary analysis of included RCT and no additional information provided*
Danhof, N A, van Eekelen, R, Repping, S et al. (2019) Follicle stimulating hormone or clomiphene citrate in intrauterine insemination with ovarian stimulation for unexplained subfertility: a role for treatment selection markers?. Reproductive biomedicine online 38(6): 938-942	- Study design not in PICO *Secondary analysis of included RCT and no additional data provided*
Danhof, N A, Wang, R, van Wely, M et al. (2020) IUI for unexplained infertility-a network meta-analysis. Human reproduction update 26(1): 1-15	- Systematic review, included studies checked for relevance
Danhof, Noor A, van Wely, Madelon, Repping, Sjoerd et al. (2020) Gonadotrophins or clomiphene citrate in couples with unexplained infertility undergoing intrauterine insemination: a cost-effectiveness analysis. Reproductive biomedicine online 40(1): 99-104	- Study design not in PICO *Secondary analysis of an included RCT, and no additional data provided*
Dare, Marianna R, Crowther, Caroline A, Dodd, Jodie M et al. (2004) Single or multiple embryo transfer following in vitro fertilisation for improved neonatal outcome: a systematic review of the	- Systematic review, included studies checked for relevance

Study	Code [Reason]
literature. The Australian & New Zealand journal of obstetrics & gynaecology 44(4): 283-91	
Duran, Hakan E, Morshedi, Mahmood, Kruger, Thinus et al. (2002) Intrauterine insemination: a systematic review on determinants of success. Human reproduction update 8(4): 373-84	- Systematic review, included studies checked for relevance
Ecochard, R, Mathieu, C, Royere, D et al. (2000) A randomized prospective study comparing pregnancy rates after clomiphene citrate and human menopausal gonadotropin before intrauterine insemination. Fertility and sterility 73(1): 90-3	- Population not in PICO *<80% of participants had unexplained infertility, and data not reported separately for them*
Eskew, Ashley M, Bedrick, Bronwyn S, Hardi, Angela et al. (2019) Letrozole Compared With Clomiphene Citrate for Unexplained Infertility: A Systematic Review and Meta-analysis. Obstetrics and gynecology 133(3): 437-444	- Systematic review, included studies checked for relevance
Forman, Eric J, Hong, Kathleen H, Ferry, Kathleen M et al. (2013) In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertility and sterility 100(1): 100-7e1	- Intervention not in PICO *ICSI*
Geva, E, Yovel, I, Lerner-Geva, L et al. (2000) Intrauterine insemination before transfer of frozen-thawed embryos may improve the pregnancy rate for couples with unexplained infertility: preliminary results of a randomized prospective study. Fertility and sterility 73(4): 755-60	- Not first-line treatment *Participants had prior IVF cycles*
Goto, S, Takakura, K, Nakanishi, K et al. (2001) Efficacy of clomiphene citrate and cyclofenil for infertile women with normal ovulatory cycles. Fertility and sterility 76(2): 409-411	- Study design not in PICO *Quasi-RCT*
Goverde, A J, Lambalk, C B, McDonnell, J et al. (2005) Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: effects on pregnancy and multiple pregnancy rates. Human reproduction (Oxford, England) 20(11): 3141-6	- Study design not in PICO *Secondary analysis of an included RCT and no additional data provided*
Goverde, AJ (2001) Intrauterine insemination: the treatment of choice in idiopathic and male subfertility. Biomedicine & pharmacotherapy 55(1): 70-71	- Study design not in PICO *Commentary*
Grady, Rosheen, Alavi, Nika, Vale, Rachel et al. (2012) Elective single embryo transfer and perinatal outcomes: a systematic review and meta-analysis. Fertility and sterility 97(2): 324-31	- Systematic review, included studies checked for relevance
Gunn, Deidre D and Bates, G Wright (2016) Evidence-based approach to unexplained infertility:	- Systematic review, included studies checked for relevance

Study	Code [Reason]
a systematic review. Fertility and sterility 105(6): 1566-1574e1	
Hansen, Karl R, He, Amy Linnea W, Styer, Aaron K et al. (2016) Predictors of pregnancy and live-birth in couples with unexplained infertility after ovarian stimulation-intrauterine insemination. Fertility and sterility 105(6): 1575-1583e2	- Study design not in PICO *Secondary analysis of an included RCT and no additional data reported*
Hughes, E G, Beecroft, M L, Wilkie, V et al. (2004) A multicentre randomized controlled trial of expectant management versus IVF in women with Fallopian tube patency. Human reproduction (Oxford, England) 19(5): 1105-9	- Intervention not in PICO *IVF with or without ICSI*
Hughes, Edward, Brown, Julie, Collins, John J et al. (2010) Clomiphene citrate for unexplained subfertility in women. The Cochrane database of systematic reviews: cd000057	- Systematic review, included studies checked for relevance
Ionescu, C. and Pacu, I. (2011) Ovarian stiulation with clomiphen citrat versus low dose of FSHrec follow bz IUI in unexplained infertility. Obstetrica si Ginecologie 59(3): 201-204	- Study not reported in English
Jee, Byung Chul, Ku, Seung Yup, Suh, Chang Suk et al. (2006) Use of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles: a pilot study. Fertility and sterility 85(6): 1774-7	- Study design not in PICO *Not a RCT*
Kaban, YB and Halim, B (2006) Comparative study of two aromatase inhibitors for ovarian stimulation in women with unexplained infertility. XVIII FIGO world congress of gynecology and obstetrics 4: 84	- Conference abstract *Data cannot be extracted from elsewhere (for instance, from an existing systematic review)*
Kersten, F A M, Nelen, W L D M, van den Boogaard, N M et al. (2017) Implementing targeted expectant management in fertility care using prognostic modelling: a cluster randomized trial with a multifaceted strategy. Human reproduction (Oxford, England) 32(8): 1648-1657	- Comparison not in PICO *Implementation strategy versus treatment as usual*
Kim, CH, Kang, HJ, Kim, SR et al. (2010) Effectiveness of Soft Stimulation Protocol, Compared with Conventional GnRH Antagonist Multiple dose Protocol in Patients Undergoing Controlled Ovarian Stimulation with Intrauterine Insemination. Korean journal of reproductive medicine 37(2): 135-142	- Comparison not in PICO *Comparing different GnRH antagonist protocols*
Kjellberg, A.T.; Carlsson, P.; Bergh, C. (2006) Randomized single versus double embryo transfer: Obstetric and paediatric outcome and a cost-effectiveness analysis. Human Reproduction 21(1): 210-216	- Population not in PICO *Unclear whether participants had unexplained infertility*

Study	Code [Reason]
Leanza, V, Coco, L, Grasso, F et al. (2014) Ovulation induction with clomiphene citrate for infertile couple. Minerva ginecologica 66(3): 309-12	- Study design not in PICO *Not clear if a RCT*
Liu, Aihai, Zheng, Chao, Lang, Junzhe et al. (2014) Letrozole versus clomiphene citrate for unexplained infertility: a systematic review and meta-analysis. The journal of obstetrics and gynaecology research 40(5): 1205-16	- Systematic review, included studies checked for relevance
Liu, Z.; Tang, H.-L.; Zhai, S.-D. (2011) Aromatase inhibitors in ovulation induction for women with unexplained infertility: A systematic review. Chinese Journal of Evidence-Based Medicine 11(11): 1327-1334	- Study not reported in English
live, birth, multiple, pregnancy, Bhattacharya, S et al. (2006) A randomised trial of expectant management, clomifene and intrauterine insemination (IUI) in the treatment of infertility. Fertility sterility abstract book q102: 43	- Conference abstract *Data cannot be extracted from elsewhere (for instance, from an existing systematic review)*
Lukassen, H G M, Braat, D D, Wetzels, Alex M M et al. (2005) Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. Human reproduction (Oxford, England) 20(3): 702-8	- Intervention not in PICO *Mixed IVF/ICSI population, disaggregated data not available and <80% received IVF without ICSI*
M Isa, Ahmed, Abu-Rafea, Basim, Al-Asiri, Sahel et al. (2014) Ovarian stimulation medications and patients' responses as prognostic factors in IUI-treated infertile Saudi patients. Iranian journal of reproductive medicine 12(7): 493-8	- Comparison not in PICO *Comparison between different gonadotropins*
Magsi, S., Lashari, S., Shaikh, R. et al. (2022) Unexplained Infertility: Comparison of Efficacy of Letrozole and Clomiphene Citrate. Pakistan Journal of Medical and Health Sciences 16(3): 109-111	- Study design not in PICO *Paper reports that participants 'randomly allocated' into groups but also reports that study design is 'prospective observational' and no detail of randomisation method so does not appear to be RCT*
Mahmood, D.J.; Abdulhameed, W.A.; Hussaini, H.A. (2020) Comparison of the effect of clomiphene citrate and letrozole on the corpus luteum and perifolliculer blood flow measured by coloured and pulsed doppler sonography. International Journal of Pharmaceutical Research 12(supplement1): 1727-1733	- Study design not in PICO *Participants randomly selected from among patients attending fertility clinic but the population does not appear to have been randomly allocated to groups*
Manders, Marlies, McLindon, Luke, Schulze, Brittany et al. (2015) Timed intercourse for couples trying to conceive. The Cochrane database of systematic reviews: cd011345	- Systematic review, included studies checked for relevance
Matorras, R., Diaz, T., Corcostegui, B. et al. (2002) Ovarian stimulation in intrauterine insemination with donor sperm: A randomized study comparing clomiphene citrate in fixed protocol versus highly	- Population not in PICO *Ovarian stimulation + IUI with donor sperm for those with male infertility*

Study	Code [Reason]
purified urinary FSH. Human Reproduction 17(8): 2107-2111	
Mayor, S. (2015) Fewer live births occur with letrozole than standard therapy for unexplained infertility, study shows. BMJ (Online) 351: h5070	- Conference abstract *unable to assess risk of bias*
McLernon, D.J., Harrild, K., Bergh, C. et al. (2011) Clinical effectiveness of elective single versus double embryo transfer: Meta-analysis of individual patient data from randomised trials. BMJ 342(7787): 34	- Intervention not in PICO *43-47% of participants had ICSI*
Min, Jason K, Hughes, Ed, Young, David et al. (2010) Elective single embryo transfer following in vitro fertilization. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 32(4): 363-377	- Intervention not in PICO *IVF with or without ICSI*
Moustafa, Mohamed Khaled; Sheded, Sheded Ashour; El Aziz Mousta, Mohamed Abd (2008) Elective single embryo transfer versus double embryo transfer in assisted reproduction. Reproductive biomedicine online 17(1): 82-7	- Population not in PICO *Unclear whether participants had unexplained infertility*
Nandi, A Gudi A Shah A Hooper R Khan K Homburg R (2016) Controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) vs. In Vitro fertilization (IVF) for the first line treatment of unexplained subfertility- a randomised controlled trial. Human reproduction (Oxford, England) 31supp1: i70-i71 Abstract no: O	- Conference abstract *Data cannot be extracted from elsewhere (for instance, from an existing systematic review)*
Nandi, Anupa, Bhide, Priya, Hooper, Richard et al. (2017) Intrauterine insemination with gonadotropin stimulation or in vitro fertilization for the treatment of unexplained subfertility: a randomized controlled trial. Fertility and sterility 107(6): 1329-1335e2	- Intervention not in PICO *Mixed IVF/ICSI population, disaggregated data not available and <80% received IVF without ICSI*
Nandi, Anupa, Raja, Gangopadhyay, White, Davinia et al. (2022) Intrauterine insemination + controlled ovarian hyperstimulation versus in vitro fertilisation in unexplained infertility: a systematic review and meta-analysis. Archives of gynecology and obstetrics 305(4): 805-824	- Systematic review, included studies checked for relevance
Nappi, L. and Carriero, C. (2000) Efficacy of super ovulatory drugs and intrauterine insemination in the management of infertility. Italian Journal of Gynaecology and Obstetrics 12(4): 154-156	- Non-systematic review
Nesbit, C.B.; Blanchette-Porter, M.; Esfandiari, N. (2022) Ovulation induction and intrauterine insemination in women of advanced reproductive age: a systematic review of the literature. Journal of Assisted Reproduction and Genetics 39(7): 1445-1491	- Systematic review, included studies checked for relevance

Study	Code [Reason]
Oglak, SC, Sakar, MN, Ege, S et al. (2020) Comparison of the efficacy of letrozole and gonadotropin combination versus gonadotropin alone in intrauterine insemination cycles in patients with unexplained infertility. Eastern journal of medicine 25(3): 427-433	- Study design not in PICO *Participants received letrozole based on choice*
Pacu, I., Ionescu, C.A., Dimitriu, M. et al. (2016) Intrauterine insemination in idiopathic infertility. Archives of the Balkan Medical Union 51(3): 334-339	- Study design not in PICO *Quasi-RCT as 'takes into account the patient's wish'*
Pandian, Z. and Bhattacharya, S. (2013) IVF for unexplained infertility. Human Reproduction Update 19(5): 431	- Study design not in PICO *A summary of a meta-analysis, and no additional data provided*
Pandian, Zabeena, Bhattacharya, Siladitya, Nikolaou, Dimitrios et al. (2003) The effectiveness of IVF in unexplained infertility: a systematic Cochrane review. 2002,. Human reproduction (Oxford, England) 18(10): 2001-7	- Full text paper not available
Pandian, Zabeena; Gibreel, Ahmed; Bhattacharya, Siladitya (2015) In vitro fertilisation for unexplained subfertility. The Cochrane database of systematic reviews: cd003357	- Systematic review, included studies checked for relevance
Pandian, Zabeena, Marjoribanks, Jane, Ozturk, Ozkan et al. (2013) Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection. The Cochrane database of systematic reviews: cd003416	- Systematic review, included studies checked for relevance
Peeraer, Karen, Debrock, Sophie, De Loecker, Peter et al. (2015) Low-dose human menopausal gonadotrophin versus clomiphene citrate in subfertile couples treated with intrauterine insemination: a randomized controlled trial. Human reproduction (Oxford, England) 30(5): 1079-88	- Study design not in PICO *Randomised at the cycle level so participants could be in both arms. Cross-over trial (without first phase results)*
Polyzos, Nikolaos P, Tzioras, Spyridon, Mauri, Davide et al. (2008) Treatment of unexplained infertility with aromatase inhibitors or clomiphene citrate: a systematic review and meta-analysis. Obstetrical & gynecological survey 63(7): 472-9	- Systematic review, included studies checked for relevance
Pourali, Leila, Ayati, Sedigheh, Tavakolizadeh, Shirin et al. (2017) Clomiphene citrate versus letrozole with gonadotropins in intrauterine insemination cycles: A randomized trial. International journal of reproductive biomedicine 15(1): 49-54	- Not first-line treatment *Participants had failed to conceive after previous treatment by clomifene citrate alone*
Qin, Fei, Zhou, Yanqiong, Huan, Lu et al. (2020) Comparison of clomiphene and letrozole for superovulation in patients with unexplained infertility undergoing intrauterine insemination: A	- Systematic review, included studies checked for relevance

Study	Code [Reason]
systematic review and meta-analysis. Medicine 99(31): e21006	
Rashidi, B.H., Gharaie, M., Momeni, M. et al. (2005) A comparison of clomiphene citrate and sequential clomiphene citrate plus human menopausal gonadotropin for use in conjunction with intrauterine insemination. Acta Medica Iranica 43(3): 187-192	- Population not in PICO *Mixed population of unexplained infertility and known reasons, disaggregated data not available and <80% unexplained infertility.*
Reindollar, Richard H, Regan, Meredith M, Neumann, Peter J et al. (2010) A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertility and sterility 94(3): 888-99	- Comparison not in PICO *Compared conventional treatment course (3 cycles of clomifene + IUI, followed by 3 cycles of FSH + IUI, followed by up to 6 cycles of IVF) with accelerated treatment course (omitted the 3 cycles of FSH + IUI)*
Requena, Antonio, Herrero, Julio, Landeras, Jose et al. (2008) Use of letrozole in assisted reproduction: a systematic review and meta-analysis. Human reproduction update 14(6): 571-82	- Systematic review, included studies checked for relevance
Scholten, Irma, Moolenaar, Lobke M, Gianotten, Judith et al. (2013) Long term outcome in subfertile couples with isolated cervical factor. European journal of obstetrics, gynecology, and reproductive biology 170(2): 429-33	- Population not in PICO *Participants with an isolated cervical factor*
Sh Tehrani Nejad, Ensieh, Abediasl, Zhila, Rashidi, Batool H et al. (2008) Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphen citrate gonadotropins in controlled ovarian hyperstimulation: a prospective, simply randomized, clinical trial. Journal of assisted reproduction and genetics 25(5): 187-90	- Not first-line treatment *Participants had several timed intercourses and ovarian stimulation with clomifene citrate with or without gonadotropins at least twice prior to enrolment*
Shao, Yi-Hong and Tulandi, Togas (2019) Letrozole and Unexplained Infertility: A Contemporary Meta-analysis. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 41(6): 832-834	- Non-systematic review
Shirin, G, Mehran, A, Maryam, B et al. (2009) Comparing the effects of clomiphene-HMG and letrozole-HMG on ovulation Induction in infertile women. Journal of reproduction & infertility 10(2): 156	- Study not reported in English
Sipe, Christopher S, Davis, William A, Maifeld, Michelle et al. (2006) A prospective randomized trial comparing anastrozole and clomiphene citrate in an ovulation induction protocol using gonadotropins. Fertility and sterility 86(6): 1676-81	- Population not in PICO *People with various infertility diagnoses were included and it is not reported how many had unexplained infertility*
Soehartono, D; Primariawan, RY; Prabowo, U (2006) RCT of letrozole and clomiphene citrate among infertile women. XVIII FIGO world congress of gynecology and obstetrics 2: 35	- Conference abstract *Data cannot be extracted from elsewhere (for instance, from an existing systematic review)*

Study	Code [Reason]
Steures, P, Custers, IM, Rumste, MME et al. (2008) Pregnancy chances in couples with unexplained subfertility after initial treatment with IUI or expectant management: a follow up study of 3 years. Human reproduction. European society of human reproduction and embryology ESHRE 24th annual meeting barcelona, 6-9 july 2008 23suppl1: i25 Abstract No: O-059 Oral	- Conference abstract *Data cannot be extracted from elsewhere (for instance, from an existing systematic review)*
Steures, P, van der Steeg, JW, Hompes, PG et al. (2008) Intra-uterine insemination with controlled ovarian hyperstimulation compared to an expectant management in couples with unexplained subfertility and an intermediate prognosis: a randomised study. Nederlands tijdschrift voor geneeskunde 152(27): 1525-1531	- Study not reported in English
Steures, Pieternel, van der Steeg, Jan Willem, Hompes, Peter G A et al. (2007) The additional value of ovarian hyperstimulation in intrauterine insemination for couples with an abnormal postcoital test and a poor prognosis: a randomized clinical trial. Fertility and sterility 88(6): 1618-24	- Population not in PICO *Population are people with cervical factor and male factor subfertility*
Steures, Pieternel, van der Steeg, Jan Willem, Hompes, Peter G A et al. (2007) Effectiveness of intrauterine insemination in subfertile couples with an isolated cervical factor: a randomized clinical trial. Fertility and sterility 88(6): 1692-6	- Population not in PICO *Participants with an isolated cervical factor*
Tamajani, Z.T., Mohammadi, S.D., Gorji, M. et al. (2019) Comparison of the efficacy of letrozole versus clomiphene citrate among iranian infertile females: A systematic review and meta-analysis. Iranian Journal of Obstetrics, Gynecology and Infertility 22(7): 89-102	- Study not reported in English
Tjon-Kon-Fat, R I, Tajik, P, Zafarmand, M H et al. (2017) IVF or IUI as first-line treatment in unexplained subfertility: the conundrum of treatment selection markers. Human reproduction (Oxford, England) 32(5): 1028-1032	- Study design not in PICO *Secondary analysis of an included RCT with no additional data reported*
Tjon-Kon-Fat, R.I., Wang, R., Eijkemans, M.J.C. et al. (2017) Interventions for unexplained subfertility: A systematic review and network meta-analysis. Cochrane Database of Systematic Reviews 2017(6): cd012692	- Study design not in PICO *Study protocol*
Tjon-Kon-Fat, Raissa I, Tajik, Parvin, Custers, Inge M et al. (2016) Can we identify subfertile couples that benefit from immediate in vitro fertilisation over intrauterine insemination?. European journal of obstetrics, gynecology, and reproductive biology 202: 36-40	- Study design not in PICO *Secondary analysis of an included RCT and no additional data provided*
van Eekelen, R, Rosielle, K, van Welie, N et al. (2020) Does the effectiveness of IUI in couples with	- Intervention not in PICO

Study	Code [Reason]
unexplained subfertility depend on their prognosis of natural conception? A replication of the H2Oil study. Human reproduction open 2020(4): hoaa047	*Hysterosalpingography with oil-based versus water-based contrast*
van Eekelen, R, Tjon-Kon-Fat, R I, Bossuyt, P M M et al. (2018) Natural conception rates in couples with unexplained or mild male subfertility scheduled for fertility treatment: a secondary analysis of a randomized controlled trial. Human reproduction (Oxford, England) 33(5): 919-923	- Study design not in PICO *Secondary analysis of an included RCT and no additional data provided*
van Eekelen, R, van Geloven, N, van Wely, M et al. (2019) Is IUI with ovarian stimulation effective in couples with unexplained subfertility?. Human reproduction (Oxford, England) 34(1): 84-91	- Study design not in PICO *Cohort study*
van Eekelen, R, Wang, R, Danhof, N A et al. (2021) Cost-effectiveness of ovarian stimulation agents for IUI in couples with unexplained subfertility. Human reproduction (Oxford, England) 36(5): 1288-1295	- Study design not in PICO *Clinical data extracted from a systematic review identified (Wang 2019)*
van Rumste, Minouche M E, Custers, Inge M, van Wely, Madelon et al. (2014) IVF with planned single-embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility: an economic analysis. Reproductive biomedicine online 28(3): 336-42	- Study design not in PICO *Secondary analysis of an included RCT and no additional data provided*
van Rumste, MME, Custers, IM, Steures, P et al. (2008) Economic analysis of treatment with IUI-COH versus 6 months expectant management in couples with unexplained subfertility over a 3 year follow up. Human reproduction. European society of human reproduction and embryology ESHRE 24th annual meeting barcelona, 6-9 july 2008 23suppl1: i25-26 Abstract No: O	- Conference abstract *Data cannot be extracted from elsewhere (for instance, from an existing systematic review)*
Vaughan, Denis A, Goldman, Marlene B, Koniares, Katherine G et al. (2022) Long-term reproductive outcomes in patients with unexplained infertility: follow-up of the Fast Track and Standard Treatment Trial participants. Fertility and sterility 117(1): 193-201	- Study design not in PICO *Follow-up survey of Fast Track and Standard Treatment Trial (FASTT)*
Veltman-Verhulst, Susanne M, Hughes, Edward, Ayeleke, Reuben Olugbenga et al. (2016) Intra-uterine insemination for unexplained subfertility. The Cochrane database of systematic reviews 2: cd001838	- Systematic review, included studies checked for relevance
Wang, Rui, Danhof, Nora A, Tjon-Kon-Fat, Raissa I et al. (2019) Interventions for unexplained infertility: a systematic review and network meta-analysis. The Cochrane database of systematic reviews 9: cd012692	- Systematic review, included studies checked for relevance
Wessel, J A, Danhof, N A, van Eekelen, R et al. (2022) Ovarian stimulation strategies for	- Systematic review, included studies checked for relevance

Study	Code [Reason]
intrauterine insemination in couples with unexplained infertility: a systematic review and individual participant data meta-analysis. Human reproduction update 28(5): 733-746	
Wordsworth, S, Buchanan, J, Mollison, J et al. (2011) Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective?. Human reproduction (Oxford, England) 26(2): 369-75	- Study design not in PICO *Economic evaluation of an included RCT*
Yland, Jennifer J, Chiu, Yu-Han, Rinaudo, Paolo et al. (2022) Emulating a target trial of the comparative effectiveness of clomiphene citrate and letrozole for ovulation induction. Human reproduction (Oxford, England) 37(4): 793-805	- Study design not in PICO *A hypothetical trial*
Zolton, Jessica R, Lindner, Peter G, Terry, Nancy et al. (2020) Gonadotropins versus oral ovarian stimulation agents for unexplained infertility: a systematic review and meta-analysis. Fertility and sterility 113(2): 417-425e1	- Systematic review, included studies checked for relevance

ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; RCT: randomised controlled trial

Excluded health economic studies

Table 76: Excluded health economic studies

Study	Code [Reason]
van Rumste, Minouche M E; Custers, Inge M; van Wely, Madelon; et al. (2014) IVF with planned single-embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility: an economic analysis. Reproductive biomedicine online; vol. 28 (no. 3); 336-42	Excluded at checklisting stage - Does not meet methodological quality criteria
Elzeiny, Hossam; Garrett, Claire; Toledo, Manuela; Stern, Kate; McBain, John; Baker, Hugh William Gordo (2014) A randomised controlled trial of intra-uterine insemination versus in vitro fertilisation in patients with idiopathic or mild male infertility. The Australian & New Zealand journal of obstetrics & gynaecology; vol. 54 (no. 2); 156-61	Excluded at checklisting stage - Does not meet methodological quality criteria - Limited reporting on health economics
Fiddelers, Audrey A A; Dirksen, Carmen D; Dumoulin, John C M; et al. (2009) Cost-effectiveness of seven IVF strategies: results of a Markov decision-analytic model. Human reproduction (Oxford, England); vol. 24 (no. 7); 1648-55	Excluded at checklisting stage - Study comparing different IVF strategies - Societal perspective
Fragoulakis, Vassilis; Kourlaba, Georgia; Tarlatzis, Basil et al. (2012) Economic evaluation of	Excluded at checklisting stage

Study	Code [Reason]
alternative assisted reproduction techniques in management of infertility in Greece. ClinicoEconomics and outcomes research : CEOR; vol. 4; 185-92	- Perspective for costs a combination of private and public. Does not represent UK costs
Peeraer, Karen; Luyten, Jeroen; Tomassetti, Carla; Verschueren, Sarah et al. (2018) Cost-effectiveness of ovarian stimulation with gonadotrophin and clomiphene citrate in an intrauterine insemination programme for subfertile couples. Reproductive biomedicine online; vol. 36 (no. 3); 302-310	Excluded at checklisting stage - More applicable health economic evidence included
Pham, Clarabelle T; Karnon, Jonathan D; Norman, Robert J; Mol, Ben W (2018) Cost-effectiveness modelling of IVF in couples with unexplained infertility. Reproductive biomedicine online; vol. 37 (no. 5); 555-563	- Not an economic evaluation
Mol, B W; Bonsel, G J; Collins, J A; Wiegerinck, M A; van der Veen, F; Bossuyt, P M (2000) Cost-effectiveness of in vitro fertilization and embryo transfer. Fertility and sterility; vol. 73 (no. 4); 748-5	- Too old
Kansal-Kalra, Suleena; Milad, Magdy P; Grobman, William A (2005) In vitro fertilization (IVF) versus gonadotropins followed by IVF as treatment for primary infertility: a cost-based decision analysis. Fertility and sterility; vol. 84 (no. 3); 600-4	- Too old
Bedaiwy, Mohamed A; Forman, Rachel; Mousa, Noha A; Al Inany, Hesham G; Casper, Robert F (2006) Cost-effectiveness of aromatase inhibitor co-treatment for controlled ovarian stimulation. Human reproduction (Oxford, England); vol. 21 (no. 11); 2838-44	- Too old
Farquhar, Cynthia M; Liu, Emily; Armstrong, Sarah; Arroll, Nicola; Lensen, Sarah; Brown, Julie (2018) Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial; Lancet (London, England); vol. 391 (no. 10119); 441-450	- Not an economic evaluation
Gerli, Sandro; Bini, Vittorio; Di Renzo, Gian Carlo (2008) Cost-effectiveness of recombinant follicle-stimulating hormone (FSH) versus human FSH in intrauterine insemination cycles: a statistical model-derived analysis. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology; vol. 24 (no. 1); 18-23	- Wrong intervention / comparator
Gerli, Sandro; Casini, Maria Luisa; Unfer, Vittorio; Costabile, Loredana; Bini, Vittorio; Di Renzo, Gian Carlo (2004) Recombinant versus urinary follicle-stimulating hormone in intrauterine insemination cycles: a prospective, randomized	- Too old

Study	Code [Reason]
analysis of cost effectiveness. Fertility and sterility; vol. 82 (no. 3); 573-8	
Chambers, Georgina M; Sullivan, Elizabeth A; Shanahan, Marian et al. (2010) Is in vitro fertilisation more effective than stimulated intrauterine insemination as a first-line therapy for subfertility? A cohort analysis. The Australian & New Zealand journal of obstetrics & gynaecology; vol. 50 (no. 3); 280-8	- Wrong study design
Yu, Bo; Mumford, Sunni; Royster, G Donald 4th; Segars, James; Armstrong, Alicia Y (2014) Cost-effectiveness analysis comparing continuation of assisted reproductive technology with conversion to intrauterine insemination in patients with low follicle numbers. Fertility and sterility; vol. 102 (no. 2); 435-9	- Wrong perspective – US
Bhatt, Taimur; Baibergenova, Akerke (2008) A comparison of the cost-effectiveness of in vitro fertilization strategies and stimulated intrauterine insemination in a Canadian health economic model. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC; vol. 30 (no. 5); 411-20	- Too old
Liu, Yuan; Su, Rongjia; Wu, Yu (2020) Cumulative Live Birth Rate and Cost-Effectiveness Analysis of Gonadotropin Releasing Hormone-Antagonist Protocol and Multiple Minimal Ovarian Stimulation in Poor Responders. Frontiers in endocrinology; vol. 11; 605939	- Not an economic evaluation
Groen, Henk; Tonch, Nino; Simons, Arnold H M et al. (2013) Modified natural cycle versus controlled ovarian hyperstimulation IVF: a cost-effectiveness evaluation of three simulated treatment scenarios. Human reproduction (Oxford, England); vol. 28 (no. 12); 3236-46	- Wrong intervention / comparator
Goverde, A J; McDonnell, J; Vermeiden, J P; Schats, R; Rutten, F F; Schoemaker, J (2000) Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet (London, England); vol. 355 (no. 9197); 13-8	- Too old
Moolenaar, Lobke M; Cissen, Maarje; de Bruin, Jan Peter et al. (2015) Cost-effectiveness of assisted conception for male subfertility. Reproductive biomedicine online; vol. 30 (no. 6); 659-66	- Wrong intervention / comparator
Pashayan, Nora; Lyratzopoulos, Georgios; Mathur, Raj (2006) Cost-effectiveness of primary offer of	- Too old

Study	Code [Reason]
IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility. BMC health services research; vol. 6; 80	
Shrestha, Deekshya; La, Xiaolin; Feng, Huai L (2015) Comparison of different stimulation protocols used in in vitro fertilization: a review. Annals of translational medicine; vol. 3 (no. 10); 137	- Not an economic evaluation
Gerris, J; De Sutter, P; De Neubourg, D; Van Royen, E; Vander Elst, J et al. (2004) A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. Human reproduction (Oxford, England); vol. 19 (no. 4); 917-23	- Wrong intervention / comparator
Khair, Andrew; Brown, Tray; Markert, Marie; Barsoe, Carsten Rodseth; Daftary, Gaurang S; Heiser, Patrick W (2023) Highly Purified Human Menopausal Gonadotropin (HP-hMG) Versus Recombinant Follicle-Stimulating Hormone (rFSH) for Controlled Ovarian Stimulation in US Predicted High-Responder Patients: A Cost-Comparison Analysis. PharmacoEconomics - open; vol. 7 (no. 5); 851-860	- Wrong perspective – US
Ryan, Ginny L; Moss, Victoria; Davis, William A; Sparks, Amy E T et al. (2005) Oral ovulation induction agents combined with low-dose gonadotropin injections and intrauterine insemination: cost- and clinical effectiveness. The Journal of reproductive medicine; vol. 50 (no. 12); 943-50	- Too old
Pan, Wei; Tu, Haiting; Jin, Lei; Hu, Cheng; Li, Yuehan; Wang, Renjie; Huang, Weiming; Liao, ShuJie (2019) Decision analysis about the cost-effectiveness of different in vitro fertilization-embryo transfer protocol under considering governments, hospitals, and patient. Medicine; vol. 98 (no. 19); e15492	- Wrong perspective – non-OECD
Crawford, Sara; Boulet, Sheree L; Mneimneh, Allison S; Perkins, Kiran M et al. (2016) Costs of achieving live birth from assisted reproductive technology: a comparison of sequential single and double embryo transfer approaches. Fertility and sterility; vol. 105 (no. 2); 444-50	- Not an economic evaluation
Almaslami, Faisal; Aljunid, Syed Mohamed (2020) Cost-effectiveness of assisted reproductive technologies in Saudi Arabia: Comparing in vitro fertilization with intrauterine insemination. SAGE open medicine; vol. 8; 2050312120931988	- Wrong perspective – non-OECD

Study	Code [Reason]
Barriere, P.; Porcu-Buisson, G.; Hamamah, S. (2018) Cost-Effectiveness Analysis of the Gonadotropin Treatments HP-hMG and rFSH for Assisted Reproductive Technology in France: A Markov Model Analysis. Applied Health Economics and Health Policy; vol. 16 (no. 1); 65-77	- Wrong intervention / comparator
Kjellberg, A.T.; Carlsson, P.; Bergh, C. (2006) Randomized single versus double embryo transfer: Obstetric and paediatric outcome and a cost-effectiveness analysis; Human Reproduction; vol. 21 (no. 1); 210-216	- Too old
Braam, S.C.; Ho, V.N.A.; Pham, T.D.; Mol, B.W.; van Wely, M.; Vuong, L.N. (2021) In-vitro maturation versus IVF: a cost-effectiveness analysis; Reproductive BioMedicine Online; vol. 42 (no. 1); 143-149	- Wrong perspective – non-OECD
Gizzo, S.; Ferrando, M.; Lispi, M.; Ripellino, C.; Cataldo, N.; Buhler, K. (2018) A cost-effectiveness modeling evaluation comparing a biosimilar follitropin alfa preparation with its reference product for live birth outcome in Germany, Italy and Spain; Journal of Medical Economics; vol. 21 (no. 11); 1096-1101	- Wrong intervention / comparator
Scotland, G.S.; McLernon, D.; Kurinczuk, J.J.; McNamee, P.; Harrild, K et al. (2011) Minimising twins in in vitro fertilisation: A modelling study assessing the costs, consequences and cost-utility of elective single versus double embryo transfer over a 20-year time horizon; BJOG: An International Journal of Obstetrics and Gynaecology; vol. 118 (no. 9); 1073-1083	- Wrong intervention / comparator
Satwik, R.; Kochhar, M. (2018) Effect of simultaneously started clomiphene citrate and gonadotropins in antagonist regimes, on cumulative live births, fresh-cycle live births and cost of stimulation in IVF cycles; Journal of Obstetrics and Gynaecology Research; vol. 44 (no. 6); 1107-1117	- Wrong study design

1
2

Appendix K Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

No research recommendations were made for this review question.

Appendix L Network meta-analysis methods

Network meta-analysis methods for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Introduction

The aim of this analysis was to compare the efficacy of different assisted reproduction techniques for people with unexplained health-related fertility problems, mild endometriosis and people with a single abnormal semen parameter. Analyses were conducted for 3 outcomes: live birth, clinical pregnancy and multiple pregnancy.

In addition to an NMA of the full dataset, stratified analyses were conducted for studies with a 'mixed prognosis' population (studies that did not restrict inclusion based on prognosis) and a 'poor prognosis' population (studies that restricted inclusion based on: prediction score using the Hunault prediction model (Hunault 2004) of natural conception leading to livebirth in the next year <30%; 30-40% chance of a spontaneous ongoing pregnancy in the next 12 months; female age 38-42 years).

Interventions

Interventions were categorised according to the assisted reproduction technique (ART) and comparisons that were of interest to the guideline committee. The committee agreed that comparisons between different gonadotropins or between aromatase inhibitors were not relevant, so gonadotropins were treated as a class, and letrozole and anastrozole were grouped together. However, the committee were interested in the comparison between clomifene citrate, gonadotropins and letrozole/anastrozole and ovarian stimulation (OS) interventions and IUI + OS interventions were coded with these agents separated out. IVF interventions that included only fresh cycles and those that included fresh and frozen cycles were combined into a single IVF class.

Study interventions were classified in the NMA as shown in Table 77.

Table 77: Classification of interventions in the NMA and study intervention

Classification in the NMA (abbreviation)	Study Intervention
Expectant Management	Expectant management
	Timed intercourse
Gonadotropin + letrozole or anastrozole + IUI (Gn + nZole + IUI)	Gonadotropin + letrozole or anastrozole + IUI
Gonadotropin + clomifene citrate + IUI (Gn + ClomC + IUI)	Gonadotropin + clomifene citrate + IUI
Clomifene citrate (ClomC)	Clomifene citrate
Clomifene citrate + IUI (ClomC + IUI)	Clomifene citrate + IUI
Clomifene citrate or gonadotropin + IUI (ClomC or Gn + IUI)	Clomifene citrate or gonadotropin + IUI
Gonadotropins + IUI (Gn + IUI)	Gonadotropins + IUI
IUI without OS	IUI without OS
IVF modified natural cycle (IVF natural fresh)	IVF modified natural cycle

Classification in the NMA (abbreviation)	Study Intervention
IVF	IVF fresh
	IVF fresh + frozen
Letrozole or anastrozole (nZole)	Letrozole or anastrozole
Letrozole or anastrozole + IUI (nZole + IUI)	Letrozole or anastrozole + IUI

Initially, grouping interventions according to the maximum number of cycles that were offered (1 cycle, 2-3 cycles, and ≥4 cycles) was explored. However, the results of this analysis were implausible, as higher rates of live birth and pregnancy were observed for 2-3 cycles than for the higher number of cycles. Further investigation of these anomalous findings suggested that heterogeneity was being introduced by studies that restricted inclusion criteria to those with a poor prognosis. In order for the networks to remain connected, distinction based on the number of cycles was not used.

We used expectant management as the reference that all relative intervention effects are reported against.

Outcomes

Live birth

Data for live births was reported as number of women having a live birth in the RCTs. The probability of live birth in each arm of a trial was estimated as the number of women having a live birth divided by the total number of women in this arm. The results are presented as posterior median odds ratios and log odds ratios.

NMAs were undertaken for the full dataset (all prognosis) and for mixed and poor prognosis subgroups. The poor prognosis subgroup was where the study population was restricted to those women with a poor prognosis as determined using the Hunault prediction model (Hunault 2004). The mixed prognosis subgroup excluded those studies limited to a population with a poor prognosis.

Clinical pregnancy

Data for clinical pregnancy was reported as number of women having a clinical pregnancy in the RCTs. The probability of clinical pregnancy in each arm of a trial was estimated as the number of women having a clinical pregnancy divided by the total number of women in this arm. The results are presented as posterior median odds ratios and log odds ratios.

NMAs were undertaken for the full dataset (all prognosis) and for mixed and poor prognosis subgroups. The poor prognosis subgroup was where the study population was restricted to those women with a poor prognosis as determined using the Hunault prediction model (Hunault 2004). The mixed prognosis subgroup excluded those studies limited to a population with a poor prognosis.

Multiple Pregnancy

Data for multiple pregnancy was reported as the women having a multiple pregnancy in the RCTs. The probability of multiple pregnancy in each arm of trial was estimated as the number of women having a multiple pregnancy divided by the total number of women having a clinical pregnancy. The results are presented as posterior median odds ratios and log odds ratios.

NMAs were undertaken for the full dataset (all prognosis) and a poor prognosis subgroup. The poor prognosis subgroup was where the study population was restricted to those women

with a poor prognosis as determined using the Hunault prediction model. It was not possible to undertake an NMA for the subgroup with a mixed prognosis as the network was not connected.

NMA models

As all outcomes were dichotomous, so binomial models with logit link were used for data synthesis. Fixed and random effects models were fitted for all analyses and model choice was based on goodness of fit.

Bayesian analysis was undertaken using MCMC simulation techniques implemented in WinBUGS 1.4.3. (Lunn 2000; Spiegelhalter 2001). The full description of standard fixed and random effects models using binomial likelihood with logit link and WinBugs codes used to synthesise data be found in NICE DSU Technical Support Document 2 (Dias 2011).

Model fit statistics

Model selection was based on the posterior mean residual deviance (a measure of model fit), and the Deviance Information Criteria (DIC), where smaller values are preferred and differences of between 3-5 are considered meaningful. Model fit statistics for each NMA analysis are given in Table 78 with the chosen model highlighted in bold. The results from the selected model are reported in the main text of this evidence review.

Table 78. Model fit statistics NMA models

Model	Data points	Posterior mean residual deviance	pD	DIC	Between-study] SD (95% CrI)
Live Birth full dataset Random effects	**37**	**39.36**	**33.0**	**245.3**	**0.51 (0.19 to 1.01)**
Live Birth full dataset Fixed effects	37	59.93	24.0	256.9	-
Live Birth mixed prognosis Random effects	21	23.71	18.9	138.5	0.41 (0.02 to 1.57)
Live Birth mixed prognosis Fixed effects	**21**	**27.48**	**15.0**	**138.3**	**-**
Live Birth poor prognosis Random effects	**16**	**16.18**	**15.5**	**108.8**	**0.78 (0.24 to 2.68)**
Live Birth poor prognosis Fixed effects	16	27.39	12.0	116.5	-
Clinical pregnancy full dataset Random effects	**77**	**78.54**	**62.6**	**454.7**	**0.50 (0.30 to 0.78)**
Clinical pregnancy full dataset Fixed effects	77	122.20	47.0	482.8	-
Clinical pregnancy mixed prognosis Random effects	**61**	**60.57**	**45.6**	**340.8**	**0.32 (0.07 to 0.61)**
Clinical pregnancy mixed prognosis Fixed effects	61	73.31	38.0	345.9	-
Clinical pregnancy	**16**	**16.37**	**15.7**	**111.1**	**0.83 (0.26 to 2.83)**

Model	Data points	Posterior mean residual deviance	pD	DIC	Between-study] SD (95% CrI)
poor prognosis Random effects					
Clinical pregnancy poor prognosis Fixed effects	16	29.56	12.0	120.5	-
Multiple pregnancy full dataset Random effects	**43**	**42.36**	**33.5**	**169.8**	**1.03 (0.27 to 2.88)**
Multiple pregnancy full dataset Fixed effects	43	52.58	28.8	175.5	
Multiple pregnancy poor prognosis Random effects	13	12.97	11.4	57.6	2.38 (0.15 to 4.83)
Multiple pregnancy poor prognosis Fixed effects	**13**	**14.96**	**10.6**	**58.7**	**-**

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts and there should be no meaningful differences between these two sources of evidence. The consistency checks were undertaken by TSU and are summarised in in Appendix N.

NMA Methods References

Dias 2011

Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, 2011, last updated September 2016, available from NICE DSU Technical Support Document 2

Lunn 2000

Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility, Statistics and Computing, 10, 325-337, 2000

Spiegelhalter 2002

Spiegelhalter D, Best N, Carlin B, van der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616, 2002

Spiegelhalter 2001

Spiegelhalter DJ,Thomas, A,Best NG, et al. WinBUGS User Manual: Version 5.1.4. Cambridge: MRC Biostatistics Unit, 2001

Turner 2015

Turner R, Jackson D, Wei Y, Thompson S, Higgins J. Predictive distributions for between study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine 2015;34:984-98.

Appendix M Threshold analysis report from the NICE Guidelines Technical Support Unit (TSU)

Threshold analysis report from the NICE Guidelines TSU for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

Guidelines Technical Support Unit, University of Bristol

Beatrice C. Downing, Nicky J. Welton

Introduction

The NICE Guidelines Technical Support Unit (TSU) were asked to assess robustness of the network meta-analysis (NMA) findings using threshold analysis for the NICE guideline on fertility problems: assessment and treatment.

Threshold analysis quantifies how much the evidence could change before a recommended treatment changes, and what the new optimal treatment would be. Threshold analysis requires a clear link between the NMA results and the recommendations in order to calculate the impact of changes in study results, for example: choose the intervention with the largest estimated increase in odds of a particular outcome.

Network Meta-analyses and format of the decision

The committee discussed the NMA evidence for each outcome, but the conclusions from initial discussions were primarily based on the results for the live birth outcome, which we focus on in the threshold analyses. The committee were presented with NMA analyses for two sets of studies, described below.

Live birth, mixed prognosis

The primary network meta-analysis was run for the subset of studies where the prognosis was not explicitly poor (the mixed prognosis population).

The NMA for the live birth outcome in the mixed prognosis population included nine studies of seven treatments (Figure 66). There was no evidence of heterogeneity and so the results from the fixed effect NMA model are shown in Figure 67. There was evidence that odds of live birth were higher when receiving treatment with either IVF (treatment 6) or IUI with gonadotrophins (treatment 4) than expectant management (Figure 67). Threshold analysis was run to assess robustness of the finding that IVF was the most effective treatment at increasing the odds of live birth within the mixed prognosis population.

Figure 66: Network of evidence for odds of live birth from studies of treatments of fertility in the population with mixed prognosis.

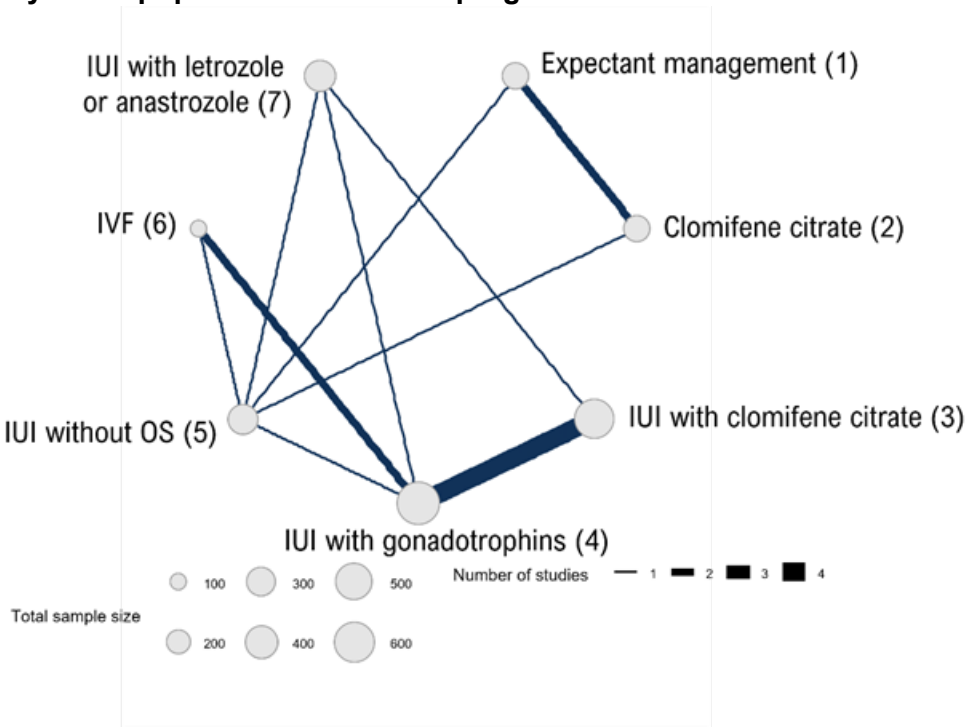
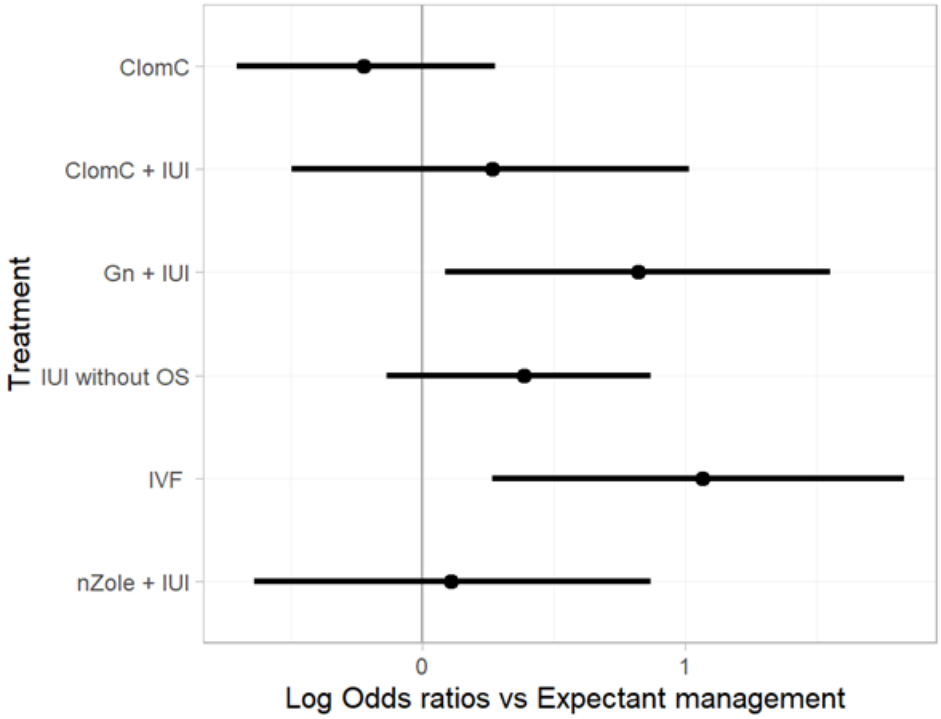


Figure 67: Estimated effect of treatment on log-odds of live birth, relative to expectant management, in dataset excluding those with explicitly poor prognosis (mixed prognosis). Where the log-odds ratio is greater than zero, odds of live birth are higher on treatment than when receiving expectant management.



Live birth, full population (any prognosis)

In a sensitivity analysis the NMA was run for the full dataset which also included the studies on patients with poor prognosis (any prognosis population).

The NMA for the live birth outcome in the full dataset for the any prognosis population included 16 studies of nine treatments (Figure 68). The NMA results for the random-effect NMA model, which was preferred on the basis of model fit statistics, are shown in Figure 69. There was evidence that odds of live birth were higher when receiving treatment with either IVF (treatment 8) or IUI with one of clomifene citrate or gonadotrophins (treatment 4) than expectant management (Figure 69). There was also weaker evidence that the odds of live birth were higher than expectant management when receiving treatment with IVF modified natural cycle (treatment 7), IUI with gonadotrophins (treatment 5) and IUI with clomifene citrate (treatment 3), though there was considerable uncertainty around the estimated treatment effect, including no difference in odds.

For this sensitivity analysis, we run a threshold analysis on the full dataset including those studies on patients with poor prognosis, to assess robustness of the finding that IVF was the most effective treatment at increasing the odds of live birth in the all prognosis population.

Figure 68: Network of evidence for odds of live birth studies of treatments of fertility in the population with any prognosis (full dataset). Treatment codes are given in parentheses.

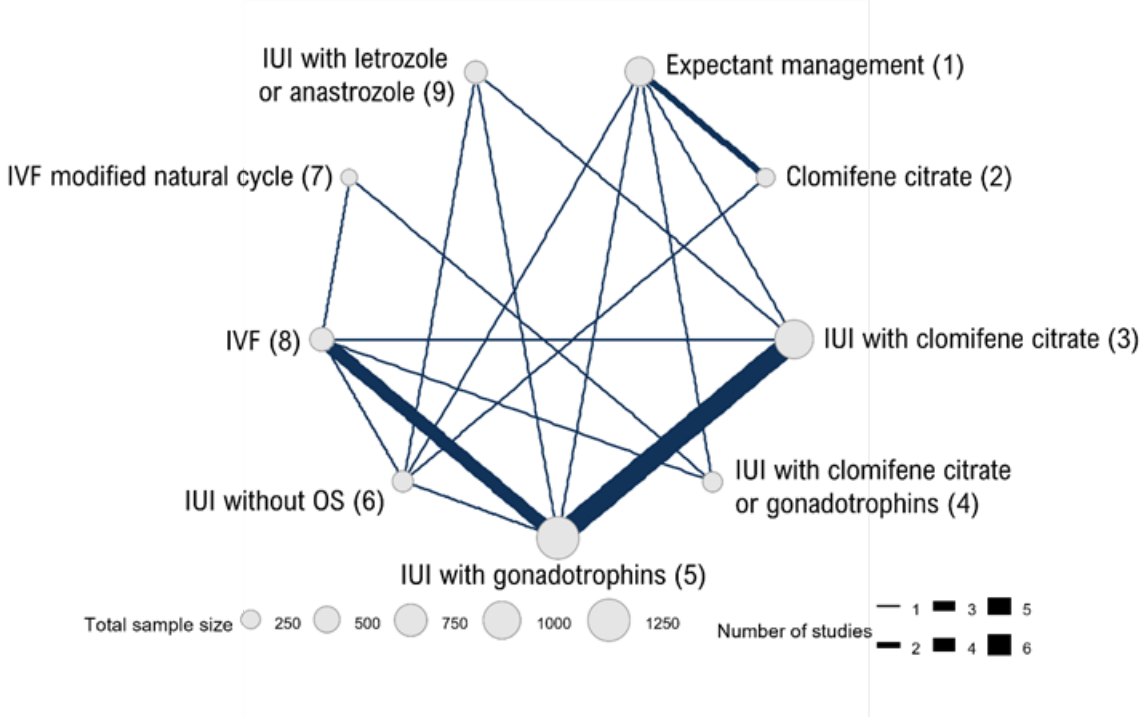


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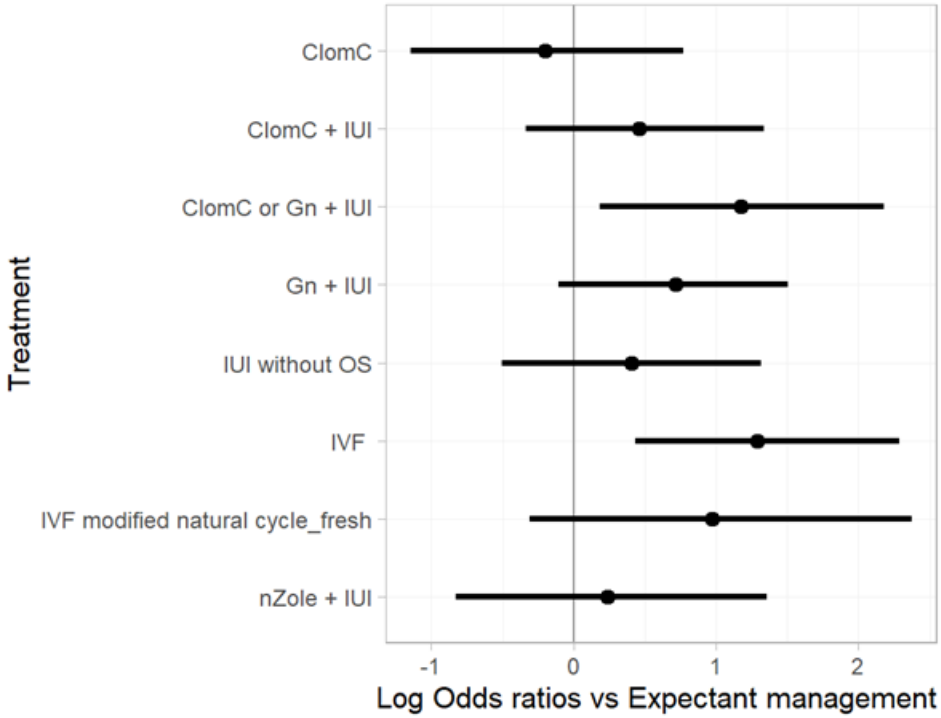
Figure 69: Estimated effect of treatment on log-odds of live birth, relative to expectant management, in full dataset (any prognosis). Where the log-odds ratio is greater than zero, odds of live birth are higher on treatment than when receiving expectant management



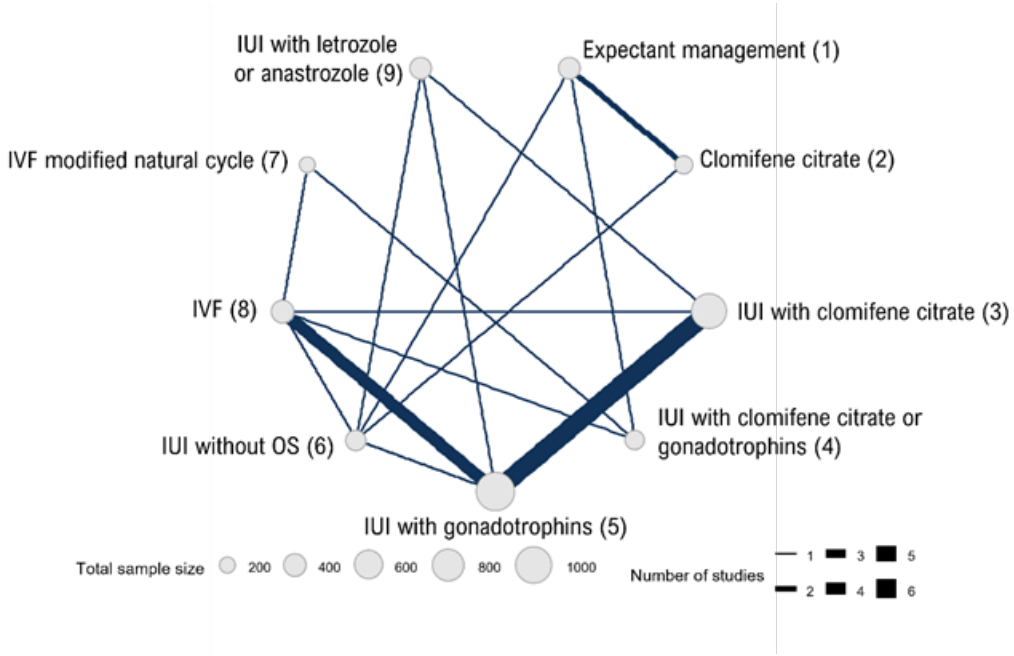
Live birth, full population (any prognosis), excluding Steures 2006 and Farquhar 2018

In the full dataset, two studies conducted in participants with poor prognosis - Steures 2006 and Farquhar 2018 - had been flagged as inconsistent with the rest of the network for both the live birth and clinical pregnancy outcomes.

An NMA of live birth in the full dataset with any prognosis, but excluding Steures and Farquhar 2018, was therefore conducted as a sensitivity analysis, including 14 studies of nine treatments (Figure 70). With these two studies removed, there was no evidence of heterogeneity and the results from the fixed effect NMA model are shown in Figure 71. There was clear evidence that odds of live birth were higher than expectant management when receiving treatment with one of IVF (treatment 8), IVF modified natural cycle (treatment 7), IUI with gonadotrophins (treatment 5) or IUI with either clomifene citrate or gonadotrophins (treatment 4) (Figure 71).

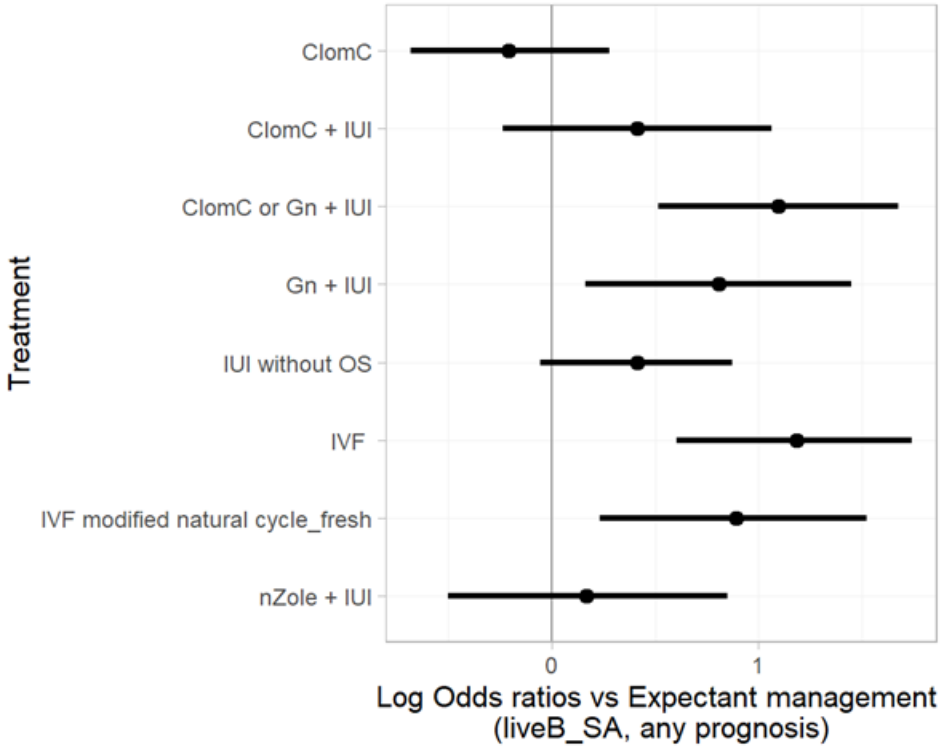
Therefore, for this sensitivity analysis a threshold analysis including 14 studies (Steures 2006 and Farquhar 2018 being dropped) using a fixed-effect NMA model, was conducted to assess robustness of the finding that IVF was the most effective treatment at increasing the odds of live birth in the all prognosis population.

Figure 70: Network of evidence for odds of live birth studies of treatments of fertility in the population with any prognosis (full dataset, excluding Farquhar 2018 and Steures 2006). Treatment codes are given in parentheses



1

Figure 71: Estimated effect of treatment on log-odds of live birth, relative to expectant management, in full dataset (any prognosis, excluding Farquhar and Steures). Where the log-odds ratio is greater than zero, odds of live birth are higher on treatment than when receiving expectant management



Methods

Threshold analysis quantifies precisely how much the evidence could change before the optimal treatment changes, and what the most effective treatment would be were the evidence to change. For each relative effect reported by a trial, the log-odds ratio is presented with its 95% confidence interval. Threshold analysis calculates the invariant interval around the effect, and highlights those where the bounds of the invariant interval fall within the confidence interval reported by the study. Threshold analysis models were run using the R package nmathresh (Phillippo et al. 2018, Phillippo et al. 2019).

Results

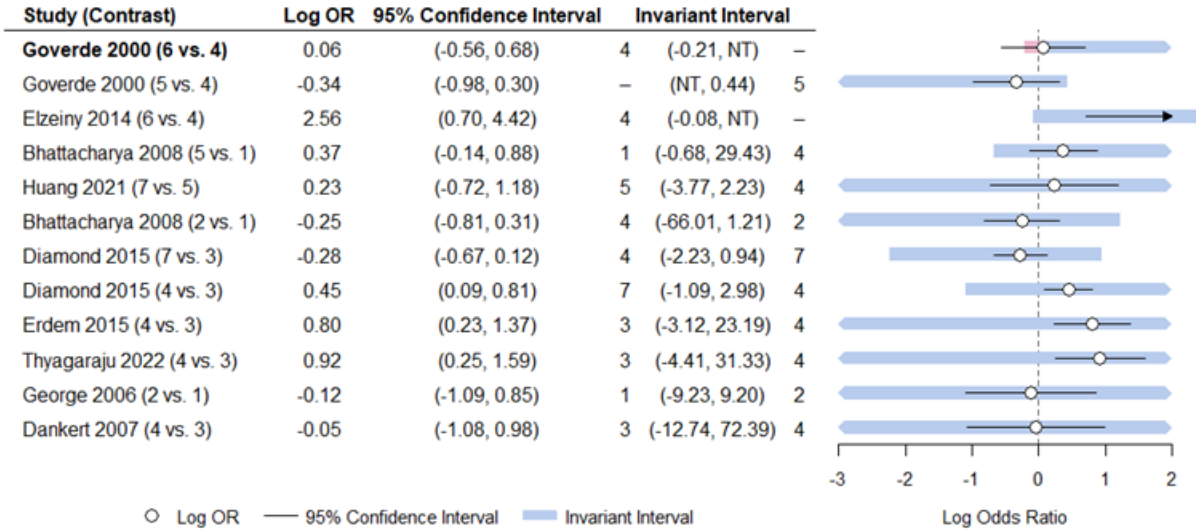
Live birth, mixed prognosis

Figure 72 shows that for most of the studies, the study estimates and confidence intervals fall easily within the invariant threshold (shaded bars), indicating that the finding that IVF is the most effective treatment (Figure 67) is robust to reasonable changes in the study estimates. However, for the Goverde 2000 study, the lower portion of the invariant interval is shaded red (and the row label is bold) as the lower threshold lies within the 95% confidence interval of the estimate from Goverde 2000; the decision is sensitive to plausible changes in this estimate. A negative change in the estimate of -0.27 would move the central estimate for IVF vs Gonadotrophin plus IUI (0.06) to the lower bound of the decision-invariant bias adjustment interval (-0.21), at which point Gonadotrophin plus IUI (treatment 4) would replace IVF

(treatment 6) as the most effective treatment. The threshold analysis highlights that the finding that IVF is the most effective treatment is sensitive to the results from Goverde 2000, with the most effective treatment changing to IUI plus gonadotrophins, with small changes in the results from Goverde 2000.

Goverde 2000 was a three-armed study trialling IVF (33 births / 87 participants) vs IUI with gonadotropins (31 births / 85 participants) vs IUI without OS (25 births / 86 participants). The overall risk of bias rating for Goverde 2000 was high – but this was not unusual in the dataset. Goverde 2000 was rated at high risk of bias in two domains: i) bias due to deviations from intended interventions (effect of assignment to intervention) and ii) bias in selection of reported result.

Figure 72: Individual study arms' influence in the finding of IVF being ranked most clinically effective: threshold analysis of live birth in the base-case analysis (mixed prognosis). Here 1 was expectant management, 2 was clomifene citrate, 3 was IUI with clomifene citrate, 4 was IUI with gonadotrophins, 5 was IUI without ovarian stimulation, 6 was IVF and 7 was IUI with letrozole or anastrozole.



Live birth, full population (any prognosis)

The threshold analysis (Figure 73) of the random-effect NMA shows that the finding that IVF (treatment 8) was the most clinically effective treatment (Figure 69) was robust to changes in many of the included studies, since the majority of study confidence intervals lie within wide invariant intervals. In seven instances, small adjustments to the treatment effect reported by the study within the confidence interval would alter the optimal treatment to IUI with clomifene citrate or gonadotropin (treatment 4).

Figure 73: Individual study arms' influence in the finding of IVF being ranked most clinically effective: threshold analysis of live birth in the full dataset (any prognosis). Here 1 was expectant management, 2 was clomifene citrate, 3 was IUI with clomifene citrate, 4 was IUI with clomifene citrate or gonadotrophins, 5 was IUI with gonadotrophins, 6 was IUI without ovarian stimulation, 7 was IVF modified natural cycle, 8 was IVF and 9 was IUI with letrozole or anastrozole.

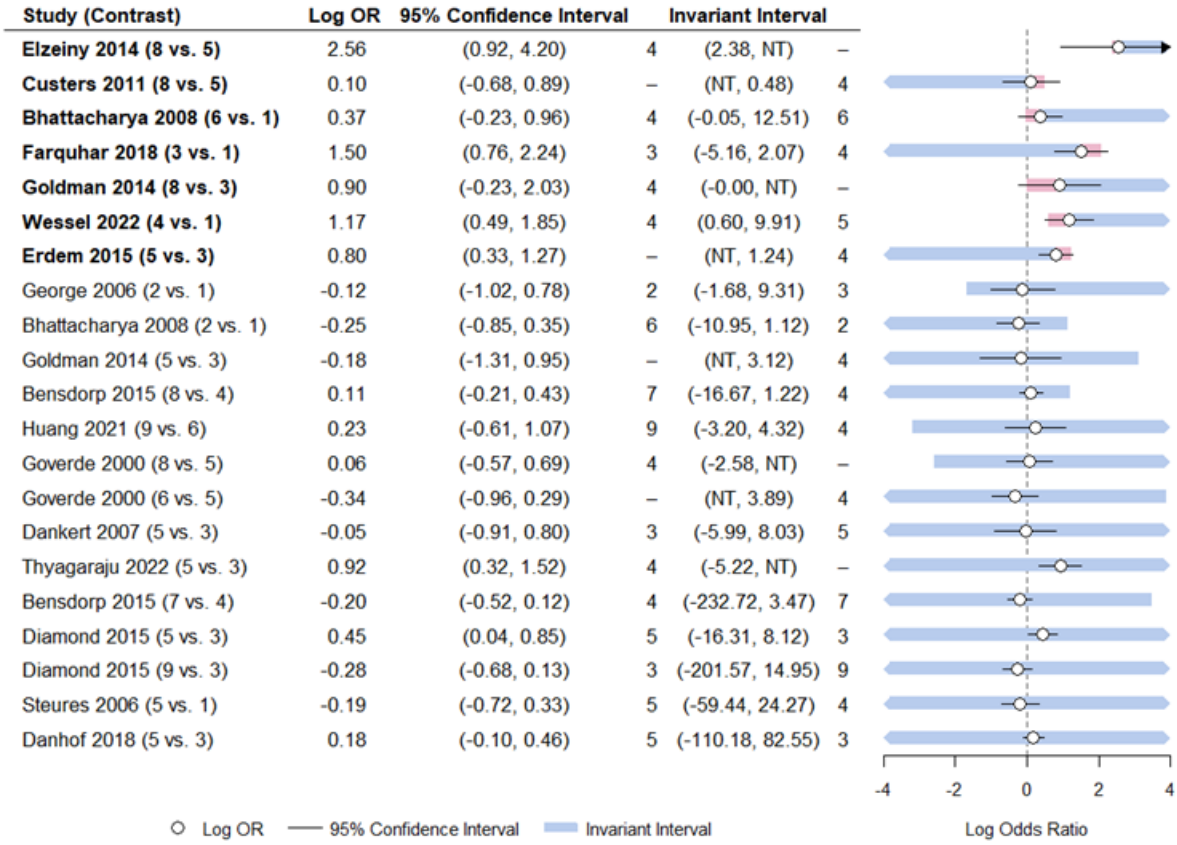


Figure 73 indicates that, for Elzeiny 2014, a reduction in the log-odds ratio of 0.18 would result in the central estimate for 'IVF vs IUI with gonadotrophin' (2.56) falling below the lower bound of the invariant interval. Similarly, for Custers 2011 an increase in the log-odds ratio of 0.38, for Farquhar 2018 an increase of 0.57 and for Erdem 2015 an increase of 0.44 would result in the central estimate of the relative effect observed in that study exceeding the upper bound of the invariant interval. A reduction in the log-odds ratio of 0.42 would result in the central estimate for 'IUI without OS vs expectant management' from Bhattacharaya 2008 (0.37), falling below the lower bound of the invariant interval. For Goldman 2014, a reduction in the log-odds ratio of 0.90 would result in the central estimate for 'IVF vs IUI with clomifene citrate' (0.90) falling below the lower bound of the invariant interval. For Wessel 2022, a reduction in the log-odds ratio of 0.57 would result in the central estimate for 'IUI with clomifene citrate or gonadotrophins vs expectant management' (1.17) falling below the lower bound of the invariant interval. In all cases, these small adjustments lie within the confidence interval for the relative treatment effect for the study arm and would result in IUI with

clomifene citrate or gonadotrophin (treatment 4) replacing IVF (treatment 8) as the most clinically effective treatment.

For Bhattacharaya 2008, a reduction in the log-odds ratio of 0.42 would result in the central estimate for 'IUI without OS vs expectant management' (0.37) falling below the lower bound of the invariant interval (0.03), which would change the most clinically effective treatment from IVF (treatment 8) to IUI with clomifene citrate or gonadotropin (treatment 4).

The overall risk of bias was judged to be high for all seven studies (Table 79): Bhattacharya 2008, Custers 2011, Elzeiny 2014, Erdem 2015, Farquhar 2018, Goldman 2014 and Wessel 2022.

Live birth, full population (any prognosis), excluding Steures 2006 and Farquhar 2018

The threshold analysis (Figure 74) shows that the finding that IVF (treatment 8) was the most clinically effective treatment was robust to changes in many of the included studies, since the majority of study confidence intervals lie within wide invariant intervals. In four instances, small adjustments to the treatment effect reported by the study within the confidence interval would alter the optimal treatment to either IUI with clomifene citrate or gonadotropin (treatment 4) or IUI with gonadotrophin (treatment 5).

Figure 9 indicates that for Elzeiny 2014, a reduction in the log-odds ratio of 0.27 would result in the central estimate for 'IVF vs IUI with gonadotrophin' (2.56) falling below the lower bound of the invariant interval. Similarly, for Custers 2011 a reduction in the log-odds ratio of 0.25 would result in the central estimate for 'IVF vs IUI with gonadotrophin' (0.10) falling below the lower bound, and a increase in the log-odds ratio of 0.39 would result in the central estimate for 'IUI without OS vs expectant management' from Bhattacharaya 2008 (0.37), exceeding the upper bound of the invariant interval. In all cases, these small adjustments lie within the confidence interval for the relative treatment effect for the study arm and would result in IUI with gonadotrophin (treatment 5) replacing IVF (treatment 8) as the most clinically effective treatment.

For Bhattacharaya 2008, a reduction in the log-odds ratio of 0.34 would result in the central estimate for 'IUI without OS vs expectant management' (0.37) falling below the lower bound of the invariant interval (0.03), which would change the most clinically effective treatment from IVF (treatment 8) to IUI with clomifene citrate or gonadotropin (treatment 4).

The overall risk of bias was judged to be high for both Bhattacharya 2008 and Elzeiny 2014 (Table 79): though Bhattacharya 2008 was at high overall risk based on high-risk on one domain (Bias due to deviations from intended interventions [effect of assignment to intervention]), while Elzeiny 2014 was at high risk of bias in one domain (Bias due to deviations from intended interventions [effect of assignment to intervention]) with some concerns in a second domain: Bias in selection of reported result.

Figure 74: Individual study arms' influence in the finding of IVF being ranked most clinically effective: threshold analysis of live birth in the full dataset, excluding Farquhar 2018 and Steures 2006 (any prognosis). Here 1 was expectant management, 2 was clomifene citrate, 3 was IUI with clomifene citrate, 4 was IUI with clomifene citrate or gonadotrophins, 5 was IUI with gonadotrophins, 6 was IUI without ovarian stimulation, 7 was IVF modified natural cycle, 8 was IVF and 9 was IUI with letrozole or anastrozole.

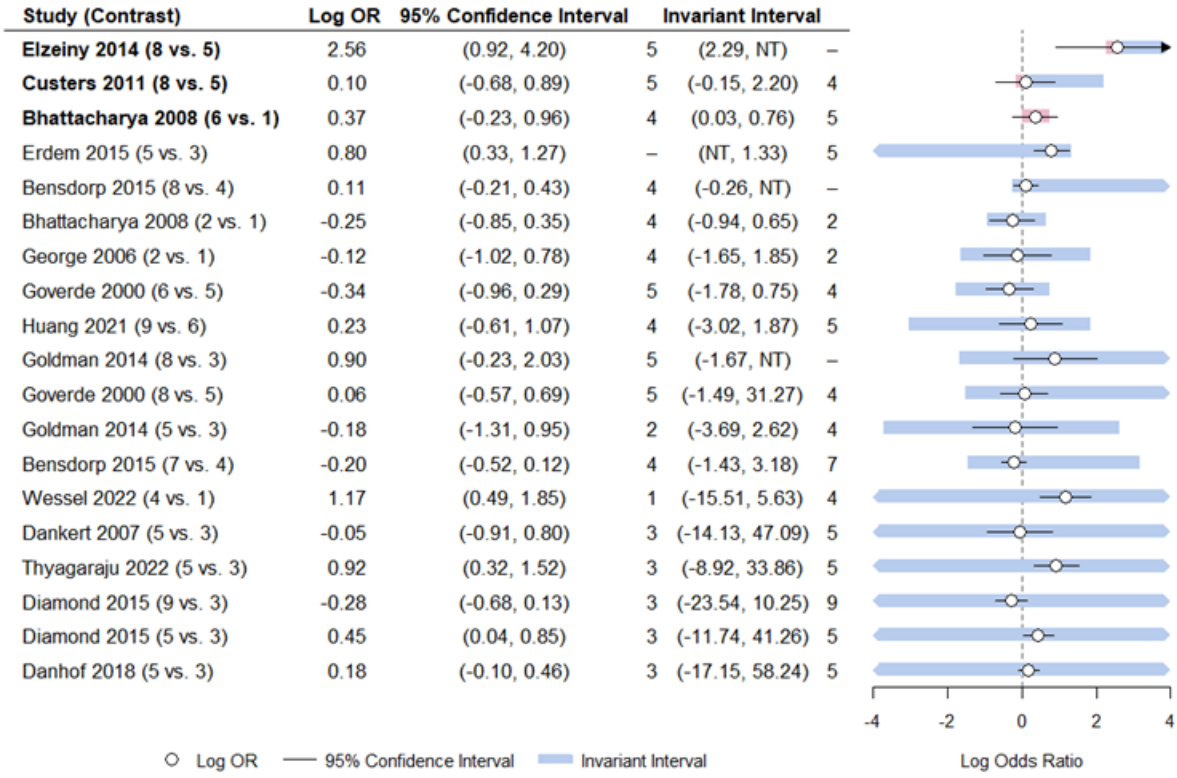


Table 79: Risk of bias assessments, selected studies, for the outcome live birth

Study ID	Cochrane v2 ROB Bias arising from randomisation	Cochrane v2 ROB Bias due to deviations from intended interventions (effect of assignment to intervention)	Cochrane v2 ROB Bias due to missing outcome data	Cochrane v2 ROB Bias in measurement of outcome	Cochrane v2 ROB Bias in selection of reported result	Cochrane v2 ROB Overall bias
Bhattacharya 2008	Low	High	Low	Low	Low	High
Custers 2011	Low	High	Low	Some concerns	Some concerns	High
Elzeiny 2014	Low	High	Low	Low	Some concerns	High

Study ID	Cochrane v2 ROB Bias arising from randomisation	Cochrane v2 ROB Bias due to deviations from intended interventions (effect of assignment to intervention)	Cochrane v2 ROB Bias due to missing outcome data	Cochrane v2 ROB Bias in measurement of outcome	Cochrane v2 ROB Bias in selection of reported result	Cochrane v2 ROB Overall bias
Erdem 2015	High	Some concerns	Low	High	Some concerns	High
Farquhar 2018	Low	High	Low	Low	Some concerns	High
Goldman 2014	Low	Low	Low	High	Some concerns	High
Wessel 2022	Low	Some concerns	High	Low	Some concerns	High

Conclusions

The finding that IVF was the most effective treatment for increasing the odds of live birth was consistent when looking at the population without an explicitly poor prognosis (mixed) and when looking across the whole population: those with poor prognosis and those with any prognosis.

Threshold analysis did reveal cases in which small changes in the findings of individual studies would change the optimal treatment from IVF to IUI with gonadotrophins (in the fixed-effect NMA model of the population with mixed prognosis) or change the optimal treatment from IVF to IUI with clomifene citrate or gonadotrophins (in the random-effect NMA model of the population with any prognosis).

References

Phillippo DM, Dias S, Ades AE, Didelez V, Welton NJ (2018). “Sensitivity of treatment recommendations to bias in network meta-analysis.” Journal of the Royal Statistical Society: Series A (Statistics in Society), 181(3), 843–867. doi:10.1111/rssa.12341

Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE. Confidence in recommendations based on Network Meta-Analysis: threshold analysis as an alternative to GRADE NMA in guideline development. Annals of Internal Medicine 2019. 170: 538-546. DOI: 10.7326/M18-3542

Appendix N Inconsistency checks

Inconsistency checks for review question: What is the clinical and cost effectiveness of ovarian stimulation, intrauterine insemination (IUI) with or without ovarian stimulation, IVF and expectant management for people with unexplained health-related fertility problems, mild endometriosis, and people with a single abnormal semen parameter?

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Introduction

The NICE Guidelines Technical Support Unit (TSU) were asked to assess validity of the consistency assumption within the network meta-analyses of three outcomes: live birth, clinical pregnancy and clinical pregnancy with multiple gestation, for the NICE guideline on fertility problems: assessment and treatment.

Data

Analyses were run on the full dataset, and also with the dataset split by patient prognosis into studies of participants with poor prognosis (poor prognosis) and studies where the prognosis was not explicitly poor (mixed prognosis).

Methods

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network. To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects (UME), model (Dias 2014). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models.

Unrelated mean effects (UME) models were fitted, and model fit and between study heterogeneity compared with the standard NMA (consistency) model, following the methods in the NICE Decision Support Unit Technical Support Document TSD4 (Dias et al. 2011, Daly et al. 2021), implemented using the R package multinma (Phillippo et al. 2020, Phillippo 2023).

Convergence was assessed by the Rhat statistic, which was required to be close to 1 (here values were within 0.01 of 1), and by ensuring that the number of effective samples exceeded 1000.

Priors

All analyses used multinma’s default priors for study-level baselines (mu_i), treatment effects (d_k), and between-study heterogeneity (τ). These specify wide prior distributions, allowing the data to inform the posterior distribution (Table 80).

Table 80: Default priors within multinma, used for the network meta-analysis of log-odds ratios (reported as the number of events in the study population) for live birth, clinical pregnancy and multiple gestation.

Priors	Range of 50% of prior distribution	Range of 95% of prior distribution
Normal distribution on study baselines $mu_i \sim N(0,100^2)$	-67.45 to 67.45	-196 to 196
Normal distribution on treatment effects (logOR scale) $d_k \sim N(0,10^2)$	-6.74 to 6.74	-19.6 to 19.6
Half-normal distribution on between-study heterogeneity $\|\tau\| \sim N(0,5^2)$	0.0 to 3.37	0.0 to 9.8

Model fit statistics

We measure model fit using the posterior mean residual deviance ($\overline{D}_{res}$) and the Deviance Information Criteria (DIC), which penalises $\overline{D}_{res}$ for complexity i.e. DIC is the sum of model fit ($\overline{D}_{res}$) and the number of effective parameters, p_D. multinma calculates DIC in this way using the posterior mean residual deviance, $\overline{D}_{res}$. However, WinBUGS calculates DIC using the posterior mean of the deviance ($\overline{D}$). Since $\overline{D}_{res}$ and $\overline{D}$ only differ by a constant, the difference in DIC between models is the same regardless of the software used for evidence synthesis.

For a well-fitting model we expect $\overline{D}_{res}$ to be similar to the number of data-points, and we prefer models with smaller $\overline{D}_{res}$ and DIC, where differences of at least three are considered meaningful. Comparing $\overline{D}_{res}$ and DIC between NMA and UME models gives a global check of the presence of inconsistency across the network. We also compare the between studies standard deviation for random effect models. Where the model fit and between studies standard deviation is similar between models, there is unlikely to be substantial inconsistency. Where model fit is relatively high in the NMA model and lower and closer to the number of data points in the UME model, or between study standard deviation is lower in the UME model, then there is likely to be inconsistency within the network.

Interpretation of dev-dev plots

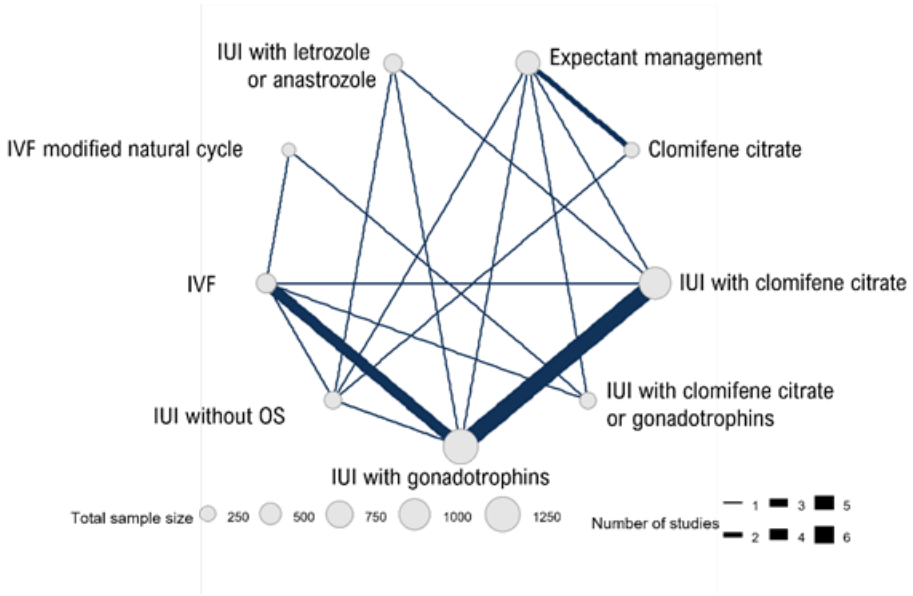
Dev-dev plots allow us to locate inconsistency associated with particular loops of evidence. Dev-dev plots display the contribution to residual deviance for each study arm under the NMA model (model 1 in dev-dev plots), which assumes consistency in treatment effects, and the UME model (model 2 in dev-dev plots), which does not. Where individual study arms are inconsistent with evidence on the other edges in the network, they appear in the lower right-hand corner of the plot, having higher residual deviance in the NMA model (model 1) than in the unrelated mean effects model (model 2).

Results

Live birth, full population (any prognosis)

Analysis of the odds of live birth included 16 studies of ten treatments (Figure 75). The model with random effects (RE) was selected on the basis of model fit, with a clear reduction in residual deviance and DIC (Table 81). The amount of variation between studies making the same treatment comparison (heterogeneity), quantified in the between-study SD, was very high: 0.50 (95% credible interval (CrI): 0.19, 1.03) on the log-odds scale.

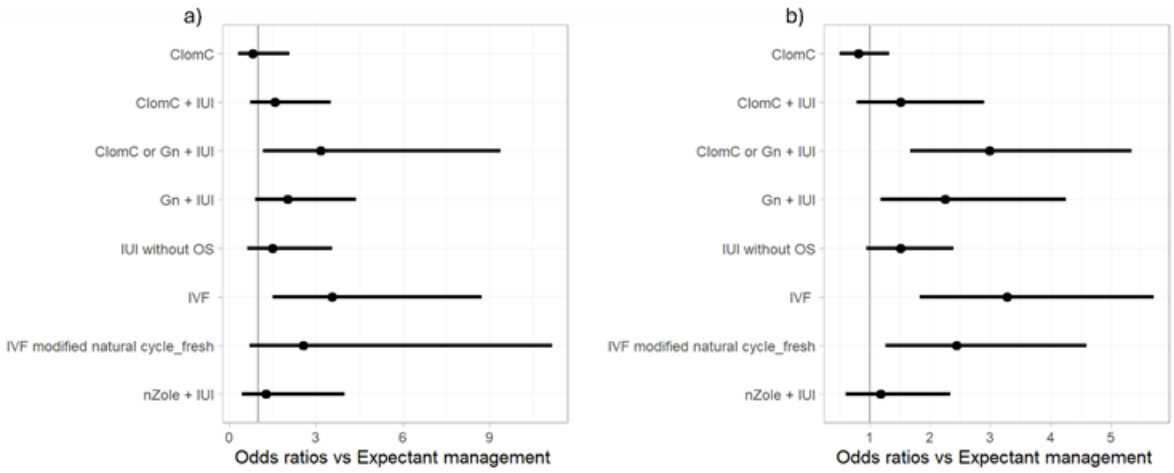
Figure 75: Network of evidence for live birth in the full dataset (any prognosis).



The between-study SD dropped substantially between random-effect (RE) NMA and RE UME models (Table 81). Penalised model fit (DIC) was equivalent between FE and RE unrelated mean effects (UME) models suggesting that, when the consistency assumption of NMA was relaxed, the model without between-study variation fitted as well as the more flexible RE UME model. Together, these suggest that, in the RE NMA, the between-study SD is inflated by inconsistency in study effects. Following examination of the fixed-effect (FE) dev-dev plot (Figure 77, panel a), this inconsistency was identified as connected with both arms of two, two-armed studies: Steures 2006 and Farquhar 2018. Both arms of Elzeiny 2014 fitted poorly in both FE and RE models; however, this was not related to inconsistency. Elzeiny 2014 was a very small study trialling IVF vs IUI with gonadotrophins that reported a relative effect for IVF that was in the same direction as that reported by other studies, though it was more extreme.

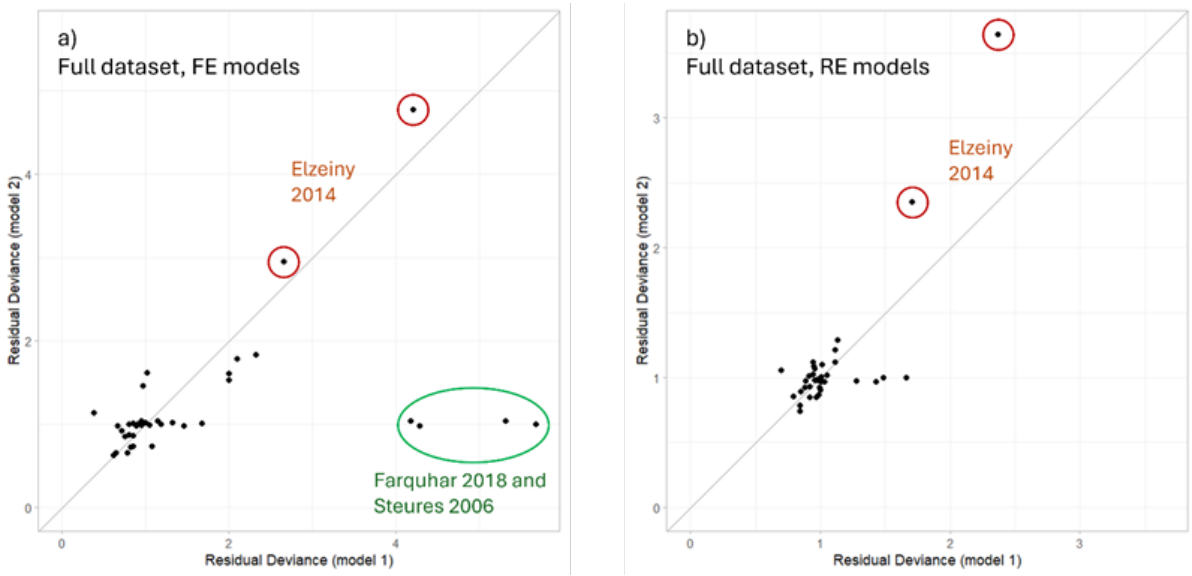
When the inconsistent studies were excluded, the FE model was preferred on model fit and the level of heterogeneity estimated within the RE model dropped substantially from 0.5 to 0.2 (Table 81). Treatment effect estimates were similar between the FE model from the dataset excluding Steures and Farquhar and the RE model of the full dataset, though the larger uncertainty present in the RE model of the full dataset translated to wider credible intervals for all treatments. The effect estimate intervals for IUI with gonadotrophins and IVF modified natural cycle included no effect relative to expectant management (Figure 76).

Figure 76: Treatment effect estimates for active treatments vs expectant management from a) RE NMA of the full dataset and b) FE NMA of the full dataset excluding Steures 2006 and Farquhar 2018. Note that horizontal axes differ between panels



1

Figure 77: Dev-dev plots for models of live birth in the full dataset: a) fixed-effects models; b) random-effects models. Both study arms of Farquhar 2018 and Steures 2006 appear to be inconsistent in the FE model.



2 ***Live birth, mixed prognosis***

3 Analysis of the odds of live birth in the dataset of studies where the participant population
4 had mixed prognosis included nine studies of seven treatments (Figure 78). The FE NMA
5 model was preferred on model fit (Table 81) and no study arms were identified as
6 inconsistent with the wider network (Figure 79).

Figure 78: Network of evidence for live birth in the population with mixed prognosis

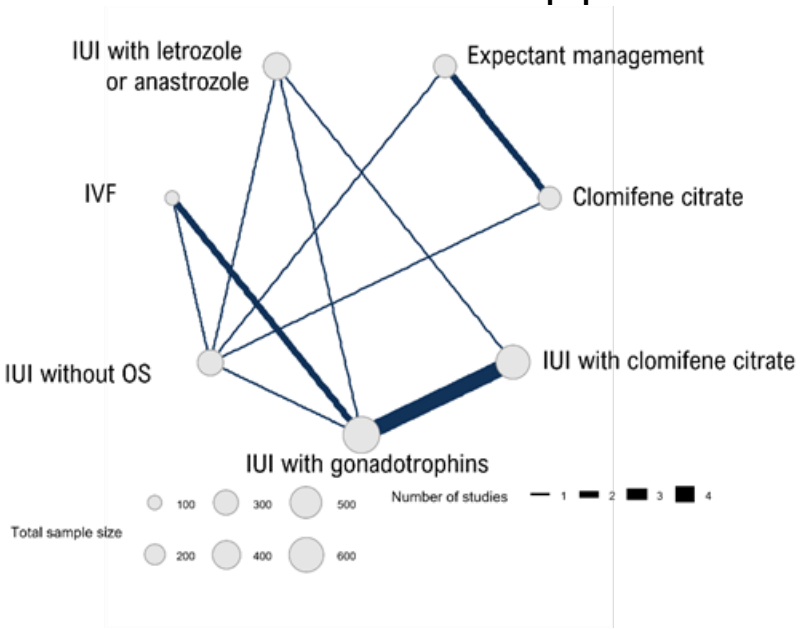


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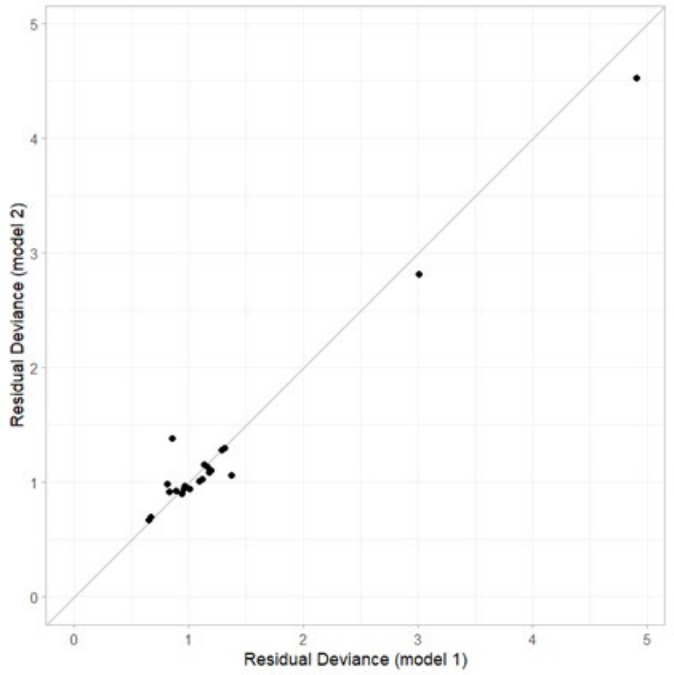
Figure 79: Dev-dev plot for FE models of live birth (mixed prognosis). No study arms appear in the lower right-hand corner, as would indicate inconsistency. Both study arms of Elzeiny 2014 fit poorly under both models and appear in the upper right-hand corner



Live birth, poor prognosis

Analysis of the odds of live birth in the dataset of studies where the participant population had poor prognosis included seven studies of six treatments (Figure 80). The RE NMA model was preferred on model fit (Table 81) and no study arms were identified as inconsistent with the wider network (Figure 81).

Figure 80: Network of evidence for live birth in the population with poor prognosis

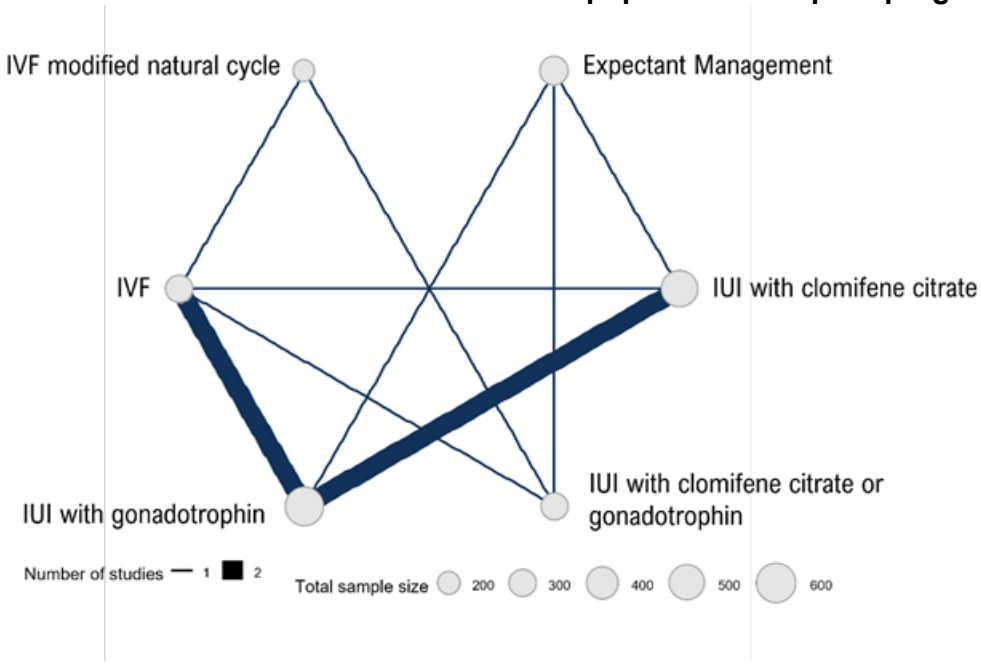


Figure 81: Dev-dev plot for FE models of live birth (poor prognosis). No study arms show high deviance under either model, or appear in the lower right-hand corner, as would indicate inconsistency

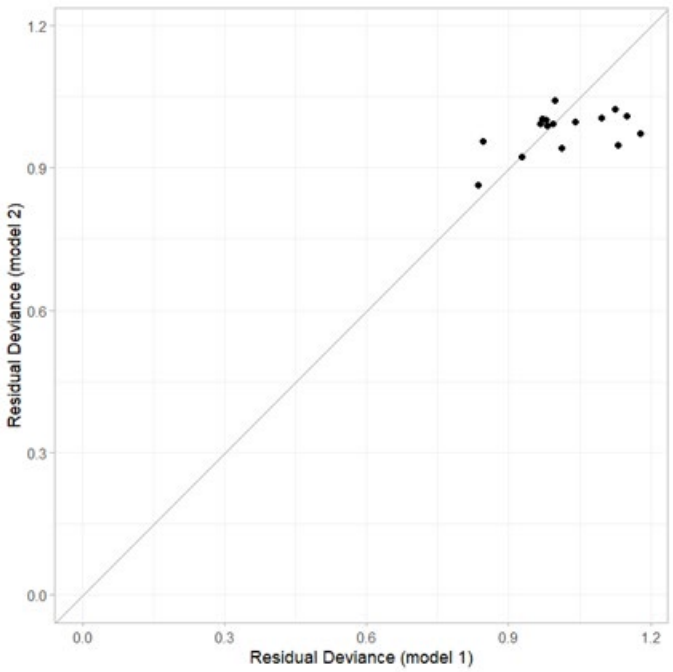


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Table 81: Model fit statistics for live birth comparing fit for models assuming consistency (NMA) and models fitting unrelated mean effects (UME) with fixed- (FE) or random-effects (RE) on treatment. In a sensitivity analysis, two inconsistent studies – Steures 2006 and Farquhar 2018 – were excluded. Models preferred on fit highlighted by grey bars.

Model		Main analysis				Sensitivity analysis			
		Data points	Posterior mean residual deviance	DIC	Between-study SD Median (95% CrI)	Posterior mean residual deviance	Posterior mean residual deviance	DIC	Between-study SD Median (95% CrI)
Full dataset	FE NMA	37	60.0	84.1	-	33	40.2	62.3	-
	RE NMA	37	39.2	72.1	0.52 (0.21, 1.00)	33	36.3	62.6	0.23 (0.01, 0.72)
	FE UME	37	44.3	73.5	-	33	40.4	65.6	-
	RE UME	37	40.4	73.6	0.39 (0.02, 0.99)	33	36.4	65.6	0.29 (0.02, 0.99)
Mixed prognosis	FE NMA	21	27.5	42.6	-	No studies excluded			
	RE NMA	21	23.7	42.7	0.41 (0.02, 1.53)	No studies excluded			
	FE UME	21	26.8	43.0	-	No studies excluded			
	RE UME	21	23.2	42.7	0.46 (0.02, 1.88)	No studies excluded			
Poor prognosis	FE NMA	16	27.3	39.3	-	12	12.3	22.4	-
	RE NMA	16	16.1	31.5	0.76 (0.24, 2.39)	12	11.9	23.4	0.57 (0.03, 3.66)
	FE UME	16	15.4	30.5	-	12	11.4	22.4	-
	RE UME	16	15.8	31.6	0.97 (0.03, 5.18)	12	11.8	23.5	0.92 (0.04, 5.51)

Clinical pregnancy, full population (any prognosis)

Analysis of clinical pregnancy in the full dataset (any prognosis) included 36 studies of 12 treatments (Figure 82). The RE NMA model was preferred on model fit (Table 82) and no study arms were identified as inconsistent with the wider network (Figure 83).

Heterogeneity decreased substantially when Steures 2006 and Farquhar 2018 (also identified as inconsistent in the analysis of the odds of live birth) were excluded; however, the RE models were still preferred on model fit, supporting the need for the model to include a parameter estimating the between-study variation.

Figure 82: Network of evidence for clinical pregnancy in the full dataset (any prognosis)

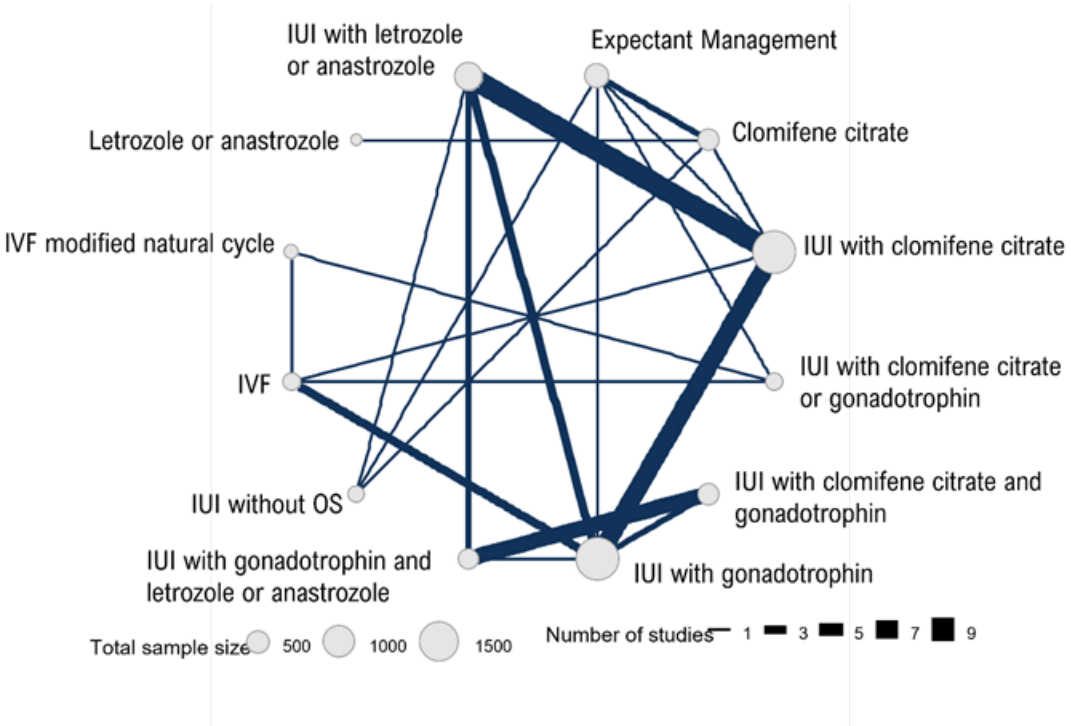
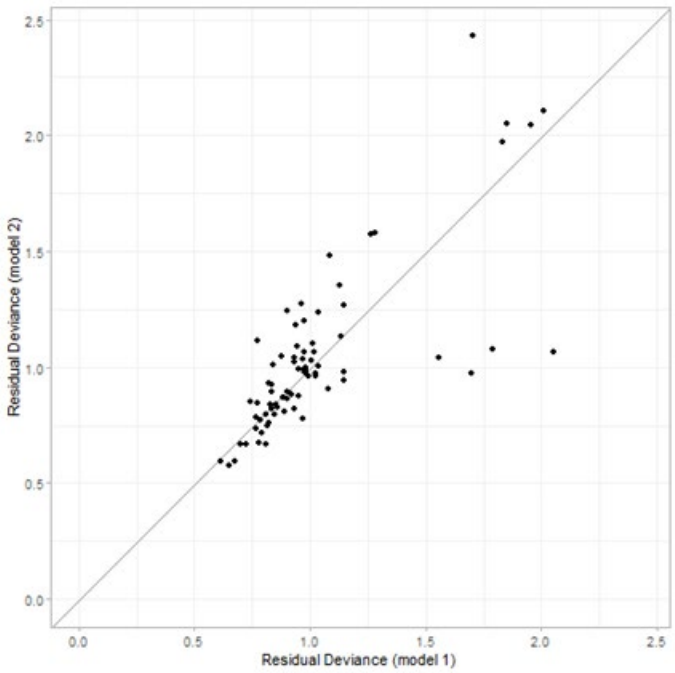


Figure 83: Dev-dev plot for RE models of clinical pregnancy in the full dataset (any prognosis). No study arms appear in the lower right-hand corner, as would indicate inconsistency



Clinical pregnancy, mixed prognosis

Analysis of the odds of clinical pregnancy in the dataset of studies where the participant population had mixed prognosis included 29 studies of 10 treatments (Figure 84). The RE NMA model was preferred on model fit (Table 82) and no study arms were identified as inconsistent with the wider network (Figure 85).

Figure 84: Network of evidence for clinical pregnancy (mixed prognosis).

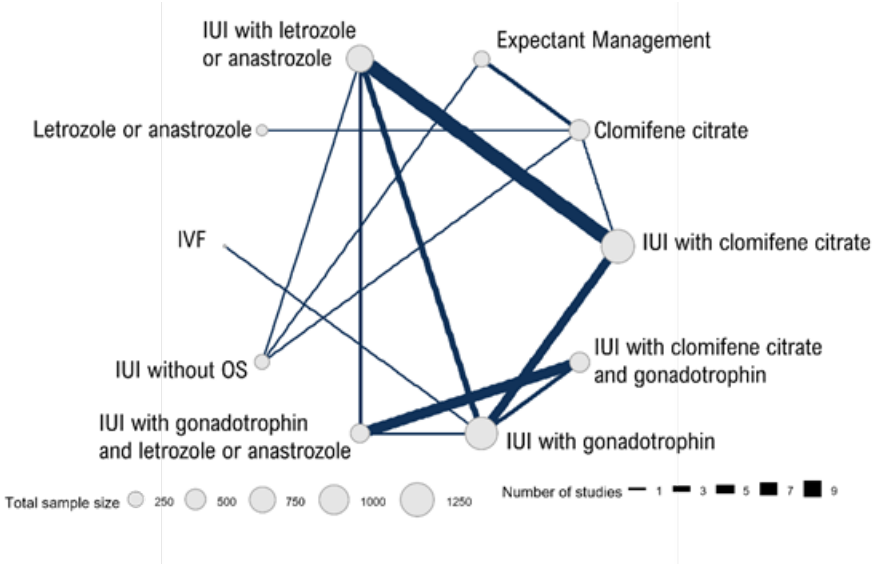
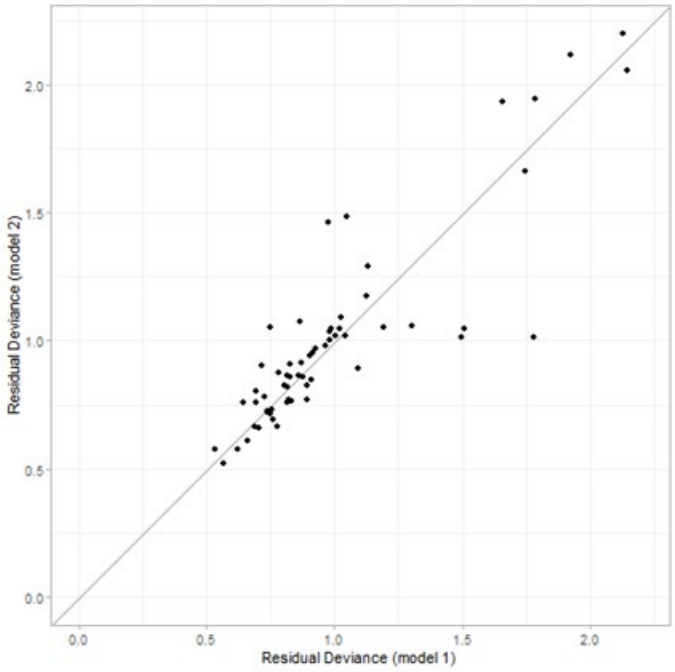


Figure 85: Dev-dev plot for RE models of clinical pregnancy (mixed prognosis). No study arms appear in the lower right-hand corner, as would indicate inconsistency



Clinical pregnancy, poor prognosis

Analysis of the odds of clinical pregnancy in the dataset of studies where the participant population had poor prognosis included seven studies of six treatments (Figure 86). The RE NMA model was preferred on model fit (Table 82), though the estimate for between-study SD was uncertain, with a wide credible interval, given the small number of repeated edges used in its estimation. No study arms were identified as inconsistent with the wider network (Figure 87); however, the unrelated mean effects (UME) models of this dataset suggest that the FE UME model fits as well as the RE UME model, and when Steures 2006 and Farquhar 2018 are excluded model fit was much improved.

Figure 86: Network of evidence for clinical pregnancy (poor prognosis).

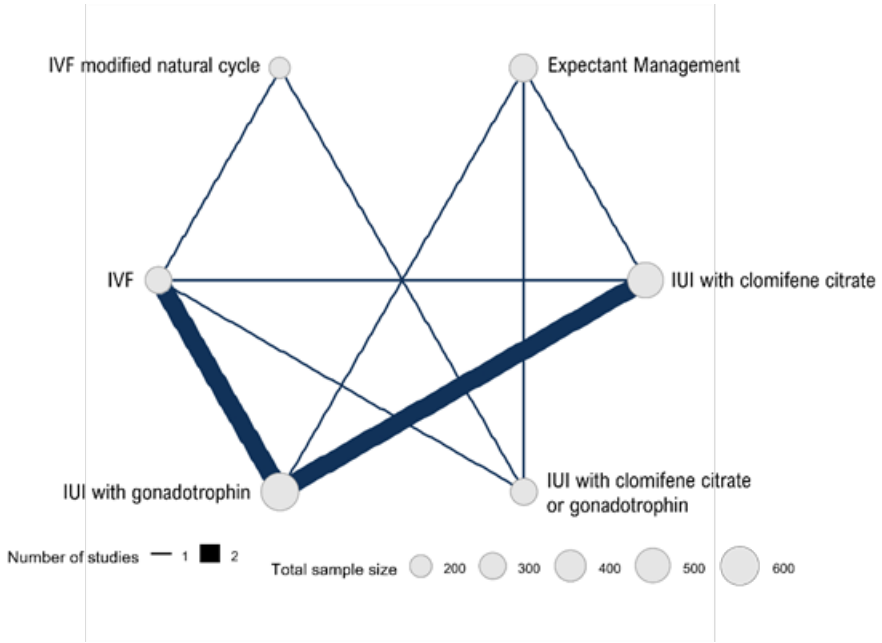


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Figure 87: Dev-dev plot for RE models of clinical pregnancy (poor prognosis). No study arms appear in the lower right-hand corner, as would indicate inconsistency

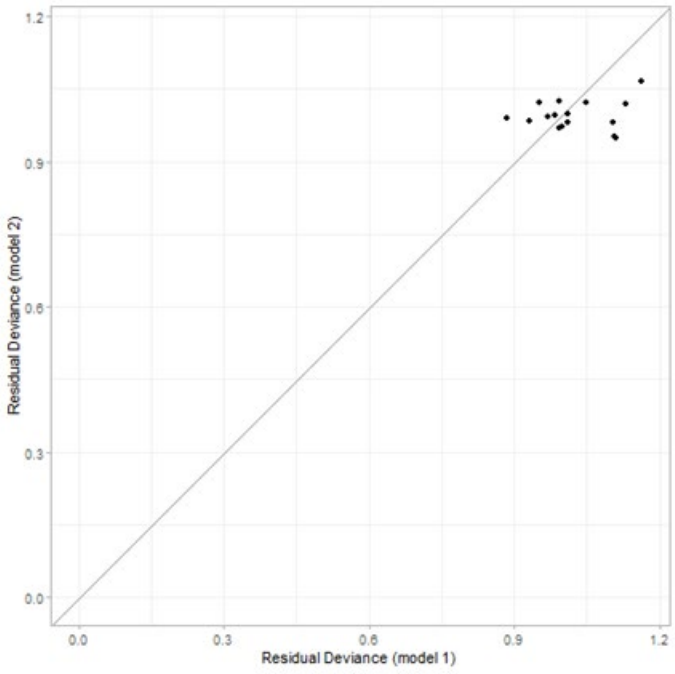


Table 82: Model fit statistics for live birth comparing fit for models assuming consistency (NMA) and models fitting unrelated mean effects (UME) with fixed- (FE) or random-effects (RE) on treatment. In a sensitivity analysis, two inconsistent studies – Steures 2006 and Farquhar 2018 – were excluded. Models preferred on fit highlighted by grey bars.

Model		Main analysis				Sensitivity analysis			
		Data points	Posterior mean residual deviance	DIC	Between-study SD Median (95% CrI)	Data points	Posterior mean residual deviance	DIC	Between-study SD Median (95% CrI)
Full dataset	FE NMA	77	122.4	170.2	-	73	96.2	141.8	-
	RE NMA	77	78.2	140.8	0.50 (0.30, 0.78)	73	74.0	130.2	0.35 (0.16, 0.63)
	FE UME	77	92.0	146.7	-	73	88.0	138.8	-
	RE UME	77	79.5	141.7	0.30 (0.08, 0.60)	73	75.8	134.1	0.29 (0.06, 0.60)
Mixed prognosis	FE NMA	61	73.4	112.1	-	No studies excluded			
	RE NMA	61	60.6	106.6	0.31 (0.09, 0.60)	No studies excluded			
	FE UME	61	66.2	107.9	-	No studies excluded			
	RE UME	61	60.7	107.3	0.23 (0.02, 0.53)	No studies excluded			
Poor prognosis	FE NMA	16	29.7	41.9	-	12	15.4	25.5	-
	RE NMA	16	16.5	32.2	0.82 (0.27, 2.61)	12	12.4	24.2	0.88 (0.06, 4.03)
	FE UME	16	15.8	30.9	-	12	11.7	22.7	-
	RE UME	16	16.0	31.9	0.88 (0.03, 5.35)	12	11.9	23.8	0.91 (0.04, 5.29)

Multiple gestation, full population (any prognosis)

Analysis of the odds of multiple gestation in the full dataset (any prognosis) included 20 studies of 12 treatments (Figure 88). The RE NMA model was preferred on model fit (Table 83), with very high heterogeneity observed: 1.01 (95% CrI: 0.25, 2.72) on the log-odds ratio scale. No study arms were identified as strongly inconsistent with the wider network (Figure 89).

Figure 88: Network of evidence for multiple gestation given clinical pregnancy in the full dataset (any prognosis).

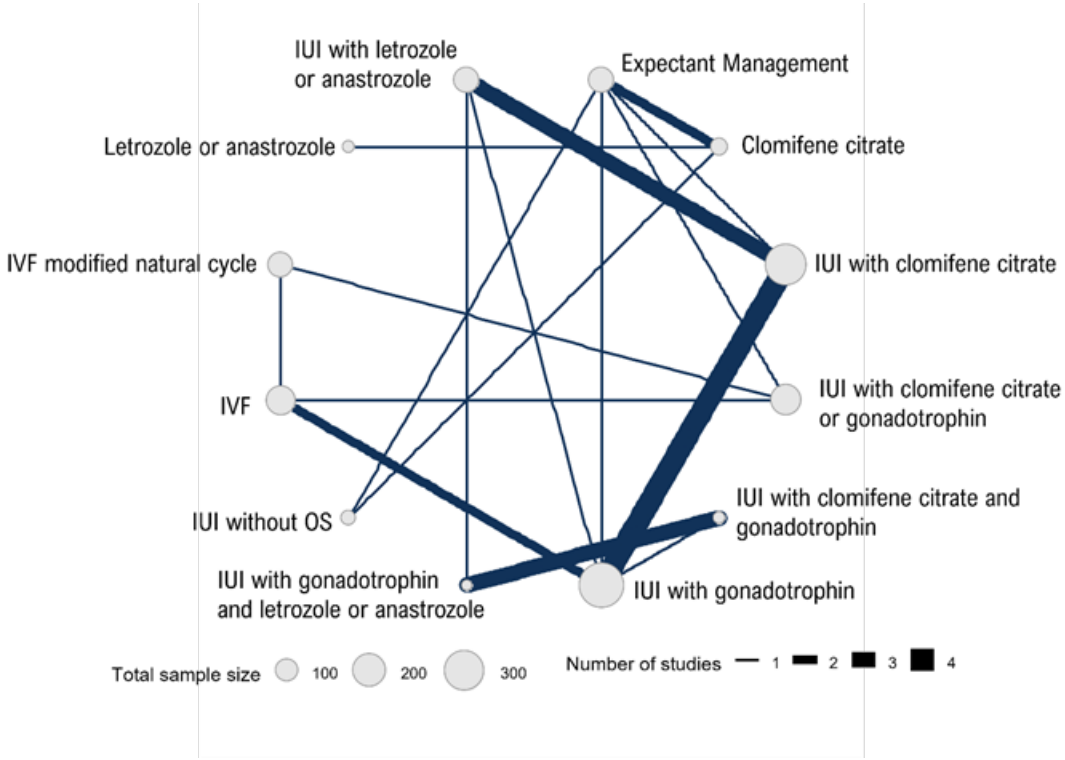
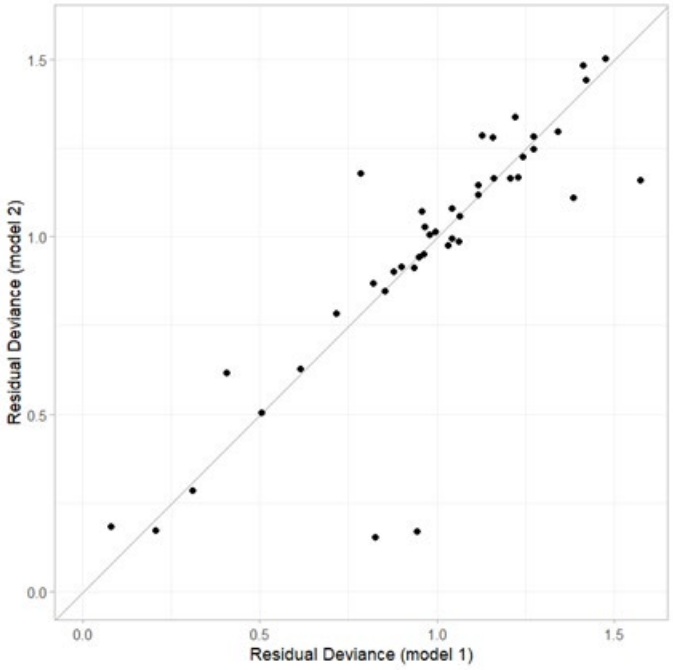


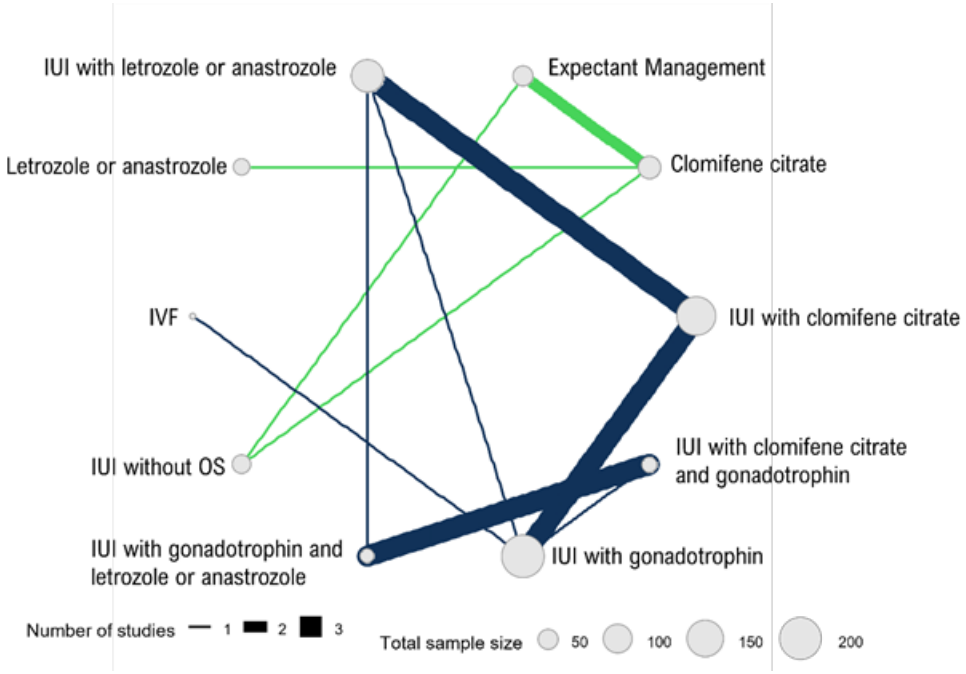
Figure 89: Dev-dev plot for RE models of multiple gestation given clinical pregnancy (any prognosis). No study arms appear in the lower right-hand corner, as would indicate inconsistency



Multiple gestation, mixed prognosis

The network of evidence was disconnected, therefore network analysis was not completed (Figure 90).

Figure 90: Network of evidence for multiple gestation given clinical pregnancy (mixed prognosis). This network was split into two components (shown in green and blue).



Multiple gestation, poor prognosis

Analysis of the odds of multiple gestation in the dataset of studies where the participant population had poor prognosis included six studies of six treatments (Figure 91). The network was formed of only one study on each arm, therefore the FE NMA model was preferred a priori. In the RE model (also fitted, Table 83), with only a single study per edge the model was unable to estimate between-study SD and the final estimate reflects the prior.

No study arms were identified as strongly inconsistent with the wider network (Figure 92). One study arm, the IUI with clomifene citrate or gonadotrophin arm of Wessel 2022, had lower posterior mean residual deviance in the UME model than under the assumption of consistency – though overall fit was reasonable under both NMA and UME models. Wessel 2022 trialled IUI with clomifene citrate or gonadotrophin against expectant management in participants with poor prognosis and reported two cases of multiple gestation on the expectant management arm (2 cases/17 clinical pregnancies) vs none on the active arm (0/37).

Figure 91: Network of evidence for multiple gestation given clinical pregnancy (poor prognosis). The edge shown in orange is the treatment comparison made by Wessel 2022, where model fit was relatively poor in the NMA, and much improved in the UME (inconsistency) model

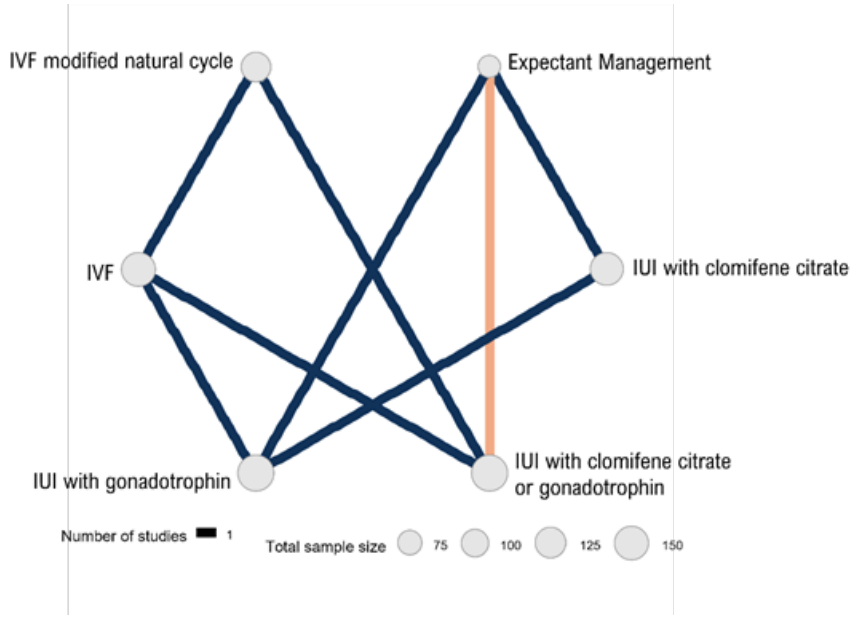


Figure 92: Dev-dev plot for FE models of multiple gestation given clinical pregnancy (poor prognosis). No study arms appear in the lower right-hand corner with high deviance in model 1 (i.e., >2), as would indicate inconsistency.

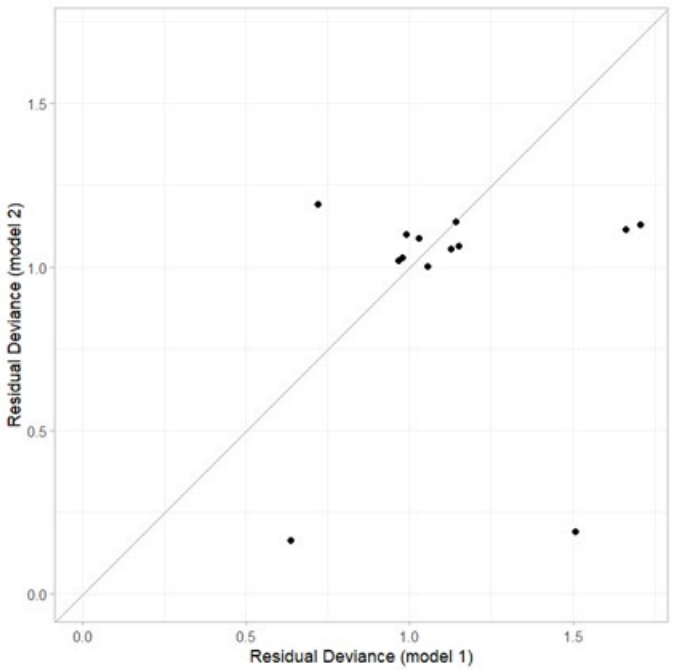


Table 83: Model fit statistics for live birth comparing fit for models assuming consistency (NMA) and models fitting unrelated mean effects (UME) with fixed- (FE) or random-effects (RE) on treatment. In a sensitivity analysis, two inconsistent studies – Steures 2006 and Farquhar 2018 – were excluded. Models preferred on fit highlighted by grey bars.

	Model	Main analysis			
		Data points	Posterior mean residual deviance	DIC	Between-study SD Median (95% CrI)
Full dataset	FE NMA	43	52.8	85.1	-
	RE NMA	43	42.4	78.2	1.01 (0.25, 2.72)
	FE UME	43	49.5	82.3	-
	RE UME	43	40.9	76.6	0.93 (0.21, 2.72)
Poor prognosis	FE NMA	13	15.0	26.4	-
	RE NMA	13	12.8	24.5	2.67 (0.14, 8.32)
	FE UME	13	11.8	23.3	-
	RE UME	13	11.7	23.1	2.44 (0.13, 8.54)

Conclusions

For the key outcome, live birth, there was no inconsistency detected in estimates from the NMA for the models preferred on the basis of model fit for each population (full dataset, mixed prognosis, or poor prognosis only). For the full dataset (including study populations with any prognosis), the RE model was preferred. This suggested that there was high between-study variation in the treatment effects, and the uncertain treatment effect estimates from NMA reflect the variation in the study population.

Upon comparing estimates of the between-study SD between NMA and UME models in the models of live birth in the full dataset, it appears that some of the uncertainty may be linked to differences related to Steures 2006 and Farquhar 2018: two studies conducted in the population with poor prognosis. When these were excluded, the between-study SD was smaller, and treatment effect estimates from NMA were similar with more precise intervals, but at the cost of excluding two studies.

For clinical pregnancy, there was no inconsistency detected in estimates from the NMA for the models preferred on the basis of model fit for each population. As with the live birth outcome, treatment effects from Steures 2006 and Farquhar 2018 fitted relatively poorly in the RE NMA in the full dataset. No study arms were noted as inconsistent in the NMA of the population with mixed prognosis.

In the outcome multiple gestation given clinical pregnancy, there was no inconsistency noted in analyses of the full population. One study, Wessel 2022, reported a treatment comparison for IUI with clomifene citrate or gonadotrophin against expectant management that was mildly inconsistent with evidence from the network in NMA of the population with poor prognosis. This study reported two pregnancies of multiple gestation in the expectant management arm vs none on the active arm, which would be inconsistent with the evidence that the odds of multiple gestation were higher on fertility treatment.

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Appendix O Acknowledgements

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