Female infertility

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ABSTRACT

INTRODUCTION: About 17% of couples in industrialised countries seek help for infertility, which may be caused by ovulatory failure, tubal damage or endometriosis, or a low sperm count. In developed countries, 80% to 90% of couples attempting to conceive are successful after 1 year and 95% after 2 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for infertility caused by ovulation disorders? What are the effects of treatments for tubal infertility? What are the effects of treatments for infertility associated with endometriosis? What are the effects of treatments for unexplained infertility? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 55 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: clomifene; drug-induced ovarian suppression; gonadotrophin priming of oocytes before in vitro maturation; gonadotrophins; gonadotrophin-releasing hormone agonists plus gonadotrophins; gonadotrophin-releasing hormone antagonists; in vitro fertilisation; intrauterine insemination alone, or combined with gonadotrophins or clomifene; laparoscopic ablation of endometrial deposits; laparoscopic ovarian drilling; laparoscopic removal; metformin; ovarian wedge biopsy; pulsatile gonadotrophin-releasing hormone; selective salpingography plus tubal catheterisation; tamoxifen; tubal flushing; and tubal surgery before in vitro fertilisation.

QUESTIONS

INTERVENTIONS

OVULATION DISORDERS: TREATMENT

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

TUBAL OBSTRUCTION: TREATMENT

Likely to be beneficial

Unknown effectiveness

ENDOMETRIOSIS: TREATMENT

Likely to be beneficial

Likely to be ineffective or harmful

UNEXPLAINED INFERTILITY: TREATMENT

Trade off between benefits and harms

Unknown effectiveness

Likely to be ineffective or harmful

Covered elsewhere in Clinical Evidence

See erectile dysfunction

See fibroids

See pelvic inflammatory disease

See varicocoele

See endometriosis

See polycystic ovary syndrome

Footnote

*No RCTs, but strong observational evidence that in vitro fertilisation increases live birth rates.

Key points

- About 17% of couples in industrialised countries seek help for infertility, which may be caused by ovulatory failure, tubal damage or endometriosis, or a low sperm count.
- In women with ovulatory disorders, clomifene and metformin increase ovulation and pregnancy rates. There is some evidence that tamoxifen may have similar efficacy to clomifene, but we found no RCTs of sufficient quality comparing tamoxifen with placebo, and it is rarely used nowadays.

  Gonadotrophins may increase pregnancy rates but may increase ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy.

  Laparoscopic ovarian drilling may be as effective as gonadotrophins.

  We don't know whether pulsed gonadotrophin-releasing hormone (GnRH), or gonadotrophin priming of oocytes before in vitro maturation increase pregnancy rates.

  Consensus suggests that in vitro fertilisation may lead to pregnancy, but increases the risks of multiple pregnancy unless single embryo replacement is practised.

  We don't know whether GnRH agonists plus gonadotrophins increase pregnancy rates compared with gonadotrophins alone but the combination treatment may be associated with an increased risk of OHSS. We don't know how effective GnRH antagonists are because we found few trials.

  We don't know whether intrauterine insemination alone, or combined with gonadotrophins or clomifene is effective for infertility caused by ovulation disorders.
- In women with tubal infertility, tubal flushing may increase pregnancy rates, with oil soluble media possibly more effective than water soluble media; however, we found few trials solely in women with tubal infertility.

  Tubal surgery before in vitro fertilisation may increase pregnancy rates compared with no treatment in women with hydrosalpinges, but we don't know whether selective salpingography plus tubal catheterisation is beneficial.

  Consensus suggests that in vitro fertilisation is beneficial.
- In women with endometriosis, adding gonadotrophins to intrauterine insemination increases live birth rates compared with no treatment and increases pregnancy rates compared with intrauterine insemination alone.

  Laparoscopic ablation of endometrial deposits may increase live birth rates compared with diagnostic laparoscopy.

  Drugs to induce ovarian suppression may not increase pregnancy rates.

  Consensus suggests that in vitro fertilisation may be beneficial.

  Tubal flushing with oil-based media may increase live birth rates and pregnancy rates in women with minimal or mild endometriosis.
- In women with unexplained infertility, clomifene does not increase live birth rates. It is not better than expectant management.

  Intrauterine insemination without ovarian stimulation does not result in a significant increase in live birth rates.

  Intrauterine insemination plus controlled ovarian stimulation may increase pregnancy rates but may increase OHSS and multiple pregnancy.

  In vitro fertilisation may be beneficial, however, evidence is insufficient to make any conclusions.

Clinical context

DEFINITION This review focuses on infertility related to factors associated with the woman rather than the man. Normal fertility has been defined as achieving a pregnancy within 2 years by regular unprotected sexual intercourse. [1] However, many define infertility as the failure to conceive after 1 year of unprotected intercourse. Infertility can be primary, in women who have never conceived, or sec-

ondary, in women who have previously conceived. This review will deal with infertility owing to endometriosis, ovulation disorders, tubal infertility, and unexplained infertility. Endometriosis is a progressive disease that occurs when the endometrial tissue lining the uterus grows outside the uterus and attaches to the ovaries, fallopian tubes, or other organs in the abdominal cavity (See endometriosis). Ovulation disorders are defined by the failure of an ovum to be expelled because of a malfunction in the ovary, and are a major cause of infertility. Tubal infertility is the inability to conceive owing to a blockage in one or both fallopian tubes, and is a common cause of infertility. Unexplained infertility is a term used to describe couples with infertility in whom standard investigations including semen analysis, tests of ovulation, and tubal patency have failed to detect any gross abnormality.

INCIDENCE/ PREVALENCE

Although there is no evidence of a major change in the prevalence of female infertility, many more couples are seeking help than previously. Currently, about 1/6 (17%) couples in industrialised countries will seek medical advice for infertility. [2] Rates of primary infertility vary widely between countries, ranging from <6% in China, Malawi, Tanzania, and Zambia; 9% in the Philippines; >10% in Finland, Sweden, and Canada; and 18% in Switzerland. [3] [4] Reported rates of secondary infertility are less reliable.

AETIOLOGY/ RISK FACTORS

In the UK, about 10% to 20% of infertility cases are unexplained. [5] The rest are caused by ovulatory failure (27%), tubal damage (14%), endometriosis (5%), low sperm count or quality (19%), and other causes (5%). [6]

PROGNOSIS

In developed countries, 80% to 90% of couples attempting to conceive are successful after 1 year and 95% after 2 years. [7] The chances of becoming pregnant vary with the cause and duration of infertility, the woman's age, the woman's previous pregnancy history, and the availability of different treatment options. [8] [9] For the first 2 to 3 years of unexplained infertility, cumulative conception rates remain high (27–46%) but decrease with increasing age of the woman and duration of infertility. [9] The background rates of spontaneous pregnancy in infertile couples can be calculated from longitudinal studies of infertile couples who have been observed without treatment. [9]

AIMS OF INTERVENTION

To achieve the delivery of one healthy baby; to reduce the distress associated with infertility, with minimal adverse effects.

OUTCOMES

Live births; **adverse effects** including miscarriages, multiple pregnancies, incidence of ovarian hyperstimulation syndrome; satisfaction with services and treatments, acceptance of childlessness if treatment is unsuccessful; **pregnancy** and **ovulation rates** are important intermediate outcomes. Spontaneous pregnancies can occur without treatment in couples who are considered infertile. [9] Effectiveness of treatments for infertility should be assessed on the basis of pregnancy rates over and above the spontaneous pregnancy rates, otherwise the impacts of treatments may be overestimated.

METHODS

Clinical Evidence search and appraisal October 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to October 2009, Embase 1980 to October 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blind, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 44). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome

of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). **Crossover design:** For infertility, RCTs with a crossover design may overestimate the treatment effect because pregnancies occurring in the first half of the trial will remove couples from the second half. [10] Crossover trials were included in some systematic reviews where no or few RCTs using a parallel group design were available. Ideally, only data from the first half of the trial, before crossover, should be used. However, post-crossover results are reported in the absence of pre-crossover results. However, a study that used a computer model to compare the results of crossover and parallel designed trials suggests that any overestimation may be clinically irrelevant. [11]

QUESTION What are the effects of treatments for infertility caused by ovulation disorders?

OPTION CLOMIFENE (CLOMIPHENE) FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Live birth rate

Compared with tamoxifen Clomifene seems as effective as tamoxifen at increasing live birth rates in anovulatory women (moderate-quality evidence).

Compared with laparoscopic ovarian drilling (LOD) We don't know whether initial treatment with clomifene or LOD is more effective at increasing live birth rates in anovulatory women (low-quality evidence).

Compared with metformin Clomifene and metformin seem equally effective at increasing live birth rates in women with polycystic ovary syndrome (PCOS) (moderate-quality evidence).

Metformin plus clomifene compared with clomifene alone Metformin plus clomifene is no more effective than clomifene alone at increasing live birth rates in women with polycystic ovary disease (high-quality evidence).

Pregnancy rate

Compared with placebo Clomifene is more effective at increasing pregnancy rates in anovulatory women or women with amenorrhoea and no other cause of infertility (high-quality evidence).

Compared with tamoxifen Clomifene seems as effective as tamoxifen at increasing pregnancy rates in anovulatory women (moderate-quality evidence).

Compared with LOD We don't know whether initial treatment with clomifene or LOD is more effective at increasing pregnancy rates in anovulatory women (low-quality evidence).

Compared with metformin We don't know how effective clomifene and metformin are compared with each other at increasing pregnancy rates in women with PCOS (low-quality evidence).

Metformin plus clomifene compared with clomifene alone We don't know whether metformin plus clomifene is more effective than clomifene alone at increasing pregnancy rates in women with polycystic ovary disease (low-quality evidence).

Compared with pulsatile gonadotrophin-releasing hormone (GnRH) We don't know how effective pulsatile GnRH plus GnRH agonist and clomifene are compared with each other at increasing pregnancy rates in women with PCOS (low-quality evidence).

Ovulation rate

Compared with placebo Clomifene is more effective at increasing ovulation rates in anovulatory women or women with amenorrhoea and no other cause of infertility (high-quality evidence).

Compared with tamoxifen Clomifene seems as effective as tamoxifen at increasing ovulation rates in anovulatory women (moderate-quality evidence).

Compared with LOD We don't know whether clomifene or LOD is more effective at increasing ovulation rates in anovulatory women (moderate-quality evidence).

Compared with metformin We don't know how effective clomifene and metformin are compared with each other at increasing ovulation rates in women with PCOS (low-quality evidence).

Metformin plus clomifene compared with clomifene alone We don't know whether metformin plus clomifene is more effective than clomifene alone at increasing ovulation rates in women with polycystic ovary disease (low-quality evidence).

Compared with pulsatile GnRH We don't know how effective pulsatile GnRH plus GnRH agonist and clomifene are compared with each other at increasing ovulation rates in women with PCOS (low-quality evidence).

Note
Clomifene has been associated with increased risks of multiple pregnancy.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Clomifene versus placebo:
We found one systematic review (search date 2009, 3 crossover RCTs, 133 women described as anovulatory or with amenorrhoea, and no other cause of infertility) comparing clomifene citrate versus placebo. [12]

The review found that clomifene (fixed dose 50 mg — variable dose up to 250 mg depending on ovulatory response; 1–5 cycles) significantly increased pregnancy rates compared with placebo (3 RCTs, post-crossover pregnancy rate: 14/70 [20%] with clomifene *v* 2/63 [3%] with placebo; OR 5.77, 95% CI 1.55 to 21.48). It also found that clomifene significantly increased ovulation rates (per woman) compared with placebo (3 RCTs, post-crossover ovulation rate: 45/70 [64%] with clomifene *v* 14/63 [22%] with placebo; fixed OR 7.47, 95% CI 3.24 to 17.23). [12] No studies were found with the outcome of live birth rate.

Clomifene versus tamoxifen:
We found one systematic review (search date 2009, 2 RCTs, 190 anovulatory women) [12] and one additional RCT [13] comparing clomifene citrate versus tamoxifen.

The review found no significant difference between clomifene and tamoxifen in rates of pregnancy or ovulation (pregnancy rate per woman: 2 RCTs: 18/97 [18.6%] with clomifene *v* 18/93 [19.4%] with tamoxifen; OR 0.94, 95% CI 0.46 to 1.94; ovulation rate per woman: 1 RCT: 30/47 [64%] with clomifene *v* 26/48 [54%] with tamoxifen; OR 1.49, 95% CI 0.66 to 3.40). [12] It found no significant difference between the treatment modalities in live birth rates (1 RCT: 1/47 [2%] with clomifene *v* 3/48 [6%] with tamoxifen; OR 0.33, 95% CI 0.03 to 3.25). [12]

The additional RCT (66 anovulatory women) found similar pregnancy rates with both treatments at 9 months (pregnancy rate: 80% in both groups; P value not reported). [13]

Clomifene versus clomifene plus tamoxifen:
See benefits of tamoxifen, p 6 .

Clomifene versus metformin:
See benefits of metformin, p 7 .

Clomifene versus clomifene plus metformin:
See benefits of metformin, p 7 .

Clomifene versus urinary human chorionic gonadotrophin (hCG) plus clomifene:
See benefits of gonadotrophins, p 11 .

Clomifene versus pulsatile gonadotrophin-releasing hormone (GnRH):
See benefits of pulsatile gonadotrophin-releasing hormone, p 17 .

Clomifene versus laparoscopic ovarian drilling (LOD):
We found one unblinded RCT (72 anovulatory women with polycystic ovary syndrome [PCOS]) comparing laparoscopic ovarian drilling (LOD) with clomifene citrate. [14] It found no significant difference between groups in the ovulation rate per person after initial treatment (24/32 [76%] with clomifene *v* 21/33 [64%] with LOD; P = 0.32). Several women from both groups subsequently received the other treatment (22/33 [67%] women who had LOD subsequently received clomifene; 11/32 [34%] women who had clomifene subsequently received LOD) because of persistence of anovulation, recurrence of anovulation, failure to conceive, or complications. The RCT found no significant difference in the proportion of pregnancies or live births within 12 months between initial treatment with clomifene and initial treatment with LOD; however, this proportion was higher with initial treatment with clomifene (pregnancy: 14/32 [44%] with clomifene *v* 9/33 [27%] with LOD; OR 2.1, 95% CI 0.7 to 5.8; P = 0.13; intention to treat analysis). [14]

Harms:

Clomifene has been associated with the well-recognised adverse effects of hot flushes, headaches, and visual complaints. [15] For information from observational studies and guidelines on multiple pregnancy, OHSS, and breast and ovarian cancer, please see comment below.

Clomifene versus placebo:
The systematic review was unable to derive information on adverse effects. [12]

Clomifene versus tamoxifen:
The systematic review was unable to provide information on the adverse effects derived from the included studies. [12] The additional RCT gave no information on adverse effects. [13]

Clomifene versus clomifene plus tamoxifen:
See harms of tamoxifen, p 6 .

Clomifene versus metformin:
See harms of metformin, p 7 .

Clomifene versus clomifene plus metformin:
See harms of metformin, p 7 .

Clomifene versus urinary hCG plus clomifene:
See harms of gonadotrophins, p 11 .

Clomifene versus pulsatile GnRH:
See harms of pulsatile gonadotrophin-releasing hormone, p 17 .

Clomifene versus LOD:
The RCT found one case of moderate ovarian hyperstimulation syndrome (OHSS), and one case of significant depression with clomifene, and one case of left-sided pelvic pain after LOD. [14]

Comment:

Multiple pregnancy: The multiple pregnancy rate in women undergoing clomifene treatment has been estimated at less than 10% of women. It is imperative that women undergoing clomifene treatment are monitored for the risk of a multiple pregnancy. [15]
Ovarian hyperstimulation syndrome: Clomifene tends to cause only mild ovarian hyperstimulation that does not require treatment. Severe OHSS is very rare after clomifene treatment. [15]
Breast and ovarian cancer: One systematic review (search date 2008, 3 cohort studies [179,534 women], 1 case-control series [4682 controls, 4575 cases]) found that the use of clomifene or gonadotrophins was not associated with a significantly increased risk of breast cancer, especially when compared with other infertile controls and adjusted for other potential confounders such as age at follow-up and family history. [16] With regard to ovarian cancers, several case-control studies published in the 1990s reported a significant increase in the risk of ovarian cancer in women receiving ovulation-stimulating drugs; however, the use of ovulation-stimulating drugs does not seem to increase the risk above baseline levels in this population. However, one non-systematic review and meta-analysis of case-control studies (8 studies, 5207 cases, 7705 controls) found an association between fertility drug use and borderline serous tumours in nulliparous women (OR 2.43, 95% CI 1.01 to 5.88). [17] As with breast cancer, increasing risk with increased duration of treatment cannot be ruled out with confidence. [16]
Clinical guide:
Guidelines from the European Society of Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) [15] and the ASRM guideline [18] on the use of clomifene citrate state that first-line treatment for an ovulatory woman with PCOS after appropriate peri-conceptual counselling and lifestyle advice is the commencement of ovulation induction with appropriate monitoring with clomifene citrate. [15] [18] However, the selection of patients for clomifene citrate treatment should take account of body weight, female age, and the presence of other infertility factors. It is recommended that the starting dose of clomifene should be 50 mg/day (for 5 days) with a maximum dose of 150 mg/day. A conception rate of up to 22% per cycle is expected in women who respond to clomifene.

OPTION TAMOXIFEN FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Live birth rate
Compared with clomifene Tamoxifen seems as effective as clomifene at increasing live birth rates in anovulatory women (moderate-quality evidence).

Pregnancy rate
Compared with clomifene Tamoxifen seems as effective as clomifene at increasing pregnancy rates in anovulatory women (moderate-quality evidence).

Ovulation rate
Compared with clomifene Tamoxifen seems as effective as clomifene at increasing ovulation rates in anovulatory women (moderate-quality evidence).

Note
We found no direct information from RCTs about whether tamoxifen is better than no active treatment in women with infertility. However, tamoxifen is rarely used in current clinical practice.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Tamoxifen versus placebo:
We found no systematic review or RCTs.

Tamoxifen versus clomifene (clomiphene):
See benefits of clomifene, p 4 .

Tamoxifen plus clomifene versus clomifene:
We found one systematic review (search date 2009), [12] which found no RCTs meeting *Clinical Evidence* inclusion criteria. It found one small unblinded RCT (see comment). [22]

Harms:

Tamoxifen versus placebo:
We found no systematic review to provide information as to the long-term risk of ovarian cancer treated with tamoxifen for ovulation induction. For further information on general harms of tamoxifen see harms of tamoxifen in reviews on Breast cancer (metastatic) and Breast cancer (non-metastatic).

Tamoxifen versus clomifene:
See harms of clomifene, p 4 .

Tamoxifen plus clomifene versus clomifene:
We found no RCTs meeting *Clinical Evidence* inclusion criteria (see comment).

Comment:

Tamoxifen plus clomifene versus clomifene:
The small unblinded RCT (20 anovulatory women) compared clomifene (100 mg during cycle days 5–9 for 3 consecutive treatment cycles) versus clomifene plus tamoxifen (clomifene 50 mg plus tamoxifen 20 mg during cycle days 5–9 for 3 consecutive treatment cycles). It found no significant difference between groups in the pre-crossover ovulation rate per woman at the end of three treatment cycles; however, this was greater with clomifene plus tamoxifen. It found that all pregnancies were normal and single, and no severe complications were associated with either of the treatments. [22]

Clinical guide:
Tamoxifen is rarely used in current clinical practice.

OPTION METFORMIN FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Live birth rate
Metformin compared with placebo We don't know how metformin and placebo/no treatment compare for increasing live birth rates in women with polycystic ovary syndrome (PCOS) (low-quality evidence).

Metformin compared with clomifene Metformin and clomifene seem equally effective at increasing live birth rates in women with PCOS (moderate-quality evidence).

Metformin plus clomifene compared with clomifene alone Metformin plus clomifene is no more effective than clomifene alone at increasing live birth rates in women with polycystic ovary disease (high-quality evidence).

Metformin plus in vitro fertilisation (IVF) compared with IVF alone Adding metformin to IVF or intracytoplasmic sperm injection (ICSI) seems no more effective than IVF or ICSI alone at increasing live birth rates (moderate-quality evidence).

Metformin compared with laparoscopic ovarian drilling (LOD) Metformin seems more effective than LOD at increasing live birth rates in women with clomifene-resistant PCOS (moderate-quality evidence).

Metformin added to LOD compared with LOD alone We don't know whether LOD followed by metformin or LOD alone is more effective in increasing live birth rates (low-quality evidence).

Metformin plus gonadotrophins compared with gonadotrophins alone We don't know whether gonadotrophins plus metformin are more effective than gonadotrophins alone at increasing live birth rate (moderate-quality evidence).

Pregnancy rate

Metformin compared with placebo Metformin is more effective than placebo at increasing pregnancy rates in women with PCOS (high-quality evidence).

Metformin compared with clomifene We don't know how effective metformin and clomifene are compared with each other at increasing pregnancy rates in women with PCOS (low-quality evidence).

Metformin plus clomifene compared with clomifene alone We don't know whether metformin plus clomifene is more effective than clomifene alone at increasing pregnancy rates in women with polycystic ovary disease (low-quality evidence).

Metformin plus IVF compared with IVF alone We don't know whether adding metformin to IVF/ICSI is more effective at increasing pregnancy rates (low-quality evidence).

Metformin compared with LOD We don't know whether metformin or LOD is more effective at increasing pregnancy rates in women with clomifene-resistant PCOS (low-quality evidence).

Metformin added to LOD compared with LOD alone We don't know whether LOD followed by metformin or LOD alone is more effective in increasing pregnancy rates (low-quality evidence).

Metformin plus gonadotrophins compared with gonadotrophins alone Gonadotrophins plus metformin may be more effective than gonadotrophins alone at increasing pregnancy rate (low-quality evidence).

Ovulation rate
Metformin compared with placebo Metformin is more effective than placebo at increasing ovulation rates in women with PCOS (high-quality evidence).

Metformin compared with clomifene We don't know how effective metformin and clomifene are compared with each other at increasing ovulation rates in women with PCOS (low-quality evidence).

Metformin plus clomifene compared with clomifene alone We don't know whether metformin plus clomifene is more effective than clomifene alone at increasing ovulation rates in women with polycystic ovary disease (low-quality evidence).

Metformin compared with LOD We don't know whether LOD or metformin is more effective at increasing ovulation rates in women with clomifene-resistant PCOS (very low-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Metformin versus placebo:
We found one systematic review (search date 2008, 16 RCTs) examining the use of metformin in women with polycystic ovary syndrome (PCOS). [19] It found that metformin significantly increased ovulation rate compared with placebo (13 RCTs: 132/445 [30%] with metformin *v* 81/430 [19%] with placebo; OR 2.12, 95% CI 1.50 to 3.00). It also found that metformin significantly increased pregnancy rate compared with placebo (6 RCTs: 56/239 [23%] with metformin *v* 18/240 [8%] with placebo; OR 3.86, 95% CI 2.18 to 6.84). The review found no significant difference between women treated with metformin or placebo in live birth rate (2 RCTs: 2/25 [8%] with metformin *v* 2/25 [8%] with placebo; OR 1.00, 95% CI 0.16 to 6.39). [19]

Metformin versus clomifene:
We found two systematic reviews (search dates 2008) comparing metformin or clomifene citrate as first-line treatment in women with PCOS. [19] [20] The systematic reviews identified the same three RCTs (850 women), however, they performed different meta-analyses, and so we have reported both here. [19] [20]

The first review (3 RCTs [all of which were identified by the second review]) found that clomifene significantly increased ovulation rate and pregnancy rate compared with metformin (3 RCTs: ovulation rate/cycle: 429/1266 [34%] with metformin *v* 617/1204 [51%] with clomifene; OR 0.48, 95% CI 0.41 to 0.57; pregnancy rate: 60/300 [20%] with metformin *v* 85/300 [28%] with clomifene; OR 0.63, 95% CI 0.43 to 0.92). It found no significant difference between metformin or clomifene for live birth rate (3 RCTs: 45/300 [15%] with metformin *v* 63/300 [21%] with clomifene; OR 0.67, 95% CI 0.44 to 1.02). [19] However, the review found significant statistical heterogeneity (P <0.01) in these analyses. Subgroup analysis according to women's BMI found that clomifene significantly increased live birth rate compared with metformin in obese women (BMI >30), however, it found that metformin significantly increased live birth rate compared with clomifene in non-obese women (BMI <30) (women with BMI >30: 2 RCTs: 19/250 [8%] with metformin *v* 54/250 [22%] with clomifene; OR 0.30, 95% CI 0.17 to 0.52; women with BMI <30: 1 RCT: 26/50 [52%] with metformin *v* 9/50 [18%] with clomifene; OR 4.94, 95% CI 1.99 to 12.26). [19]

The second review (3 RCTs [all of which were identified by the first review]) found no significant difference between groups for any outcome (ovulation rate/woman: 166/296 [56%] with metformin *v* 211/298 [71%] with clomifene; OR [clomifene *v* metformin] 1.55, 95% CI 0.40 to 5.99; clinical pregnancy rate: 59/296 [20%] with metformin *v* 84/298 [28%] with clomifene; OR [clomifene *v* metformin] 1.22, 95% CI 0.23 to 6.55; live birth rate: 44/296 [15%] with metformin *v* 62/298 [21%] with clomifene; OR [clomifene v metformin] 1.17, 95% CI 0.16 to 8.61). [20] The authors of this review commented that metformin takes longer than clomifene to work as it is altering the woman's metabolism rather than directly stimulating ovulation. [20] As a result, the number of women that ovulated is not different between the two reviews but the number of ovulatory cycles will be greater in the clomifene groups, hence explaining the apparent different results for ovulation rate between the reviews. However, the review found significant statistical heterogeneity (P <0.0001) in these analyses. It commented that differences in inclusion criteria and definition of PCOS in the RCTs, differences in BMI of women, and previous treatment history may have contributed to this heterogeneity.

Metformin plus clomifene versus clomifene alone:
We found two systematic reviews (search dates 2008) comparing clomifene plus metformin versus clomifene alone in women with PCOS, many of whom had not responded to previous treatment with clomifene. [19] [20] The systematic reviews identified three RCTs (720 people) in common, however, they applied different inclusion criteria, and reached different conclusions, so we have reported both here. We found one subsequent small RCT. [21]

The first systematic review (11 RCTs [3 RCTs also identified by the second review], 2668 people) [19] found that metformin plus ovulation induction agent (clomifene in all studies, one study additionally used human chorionic gonadotrophin) significantly improved ovulation rate compared with clomifene alone (11 RCTs: 830/1329 [70%] with metformin plus clomifene *v* 654/1339 [49%] with clomifene alone; OR 1.76, 95% CI 1.51 to 2.06). However, the review found significant statistical heterogeneity (P = 0.00003) in this analysis, which was not affected by stratification according to obesity. The review commented that it may have been caused by differences in clomifene sensitivity among study participants. The review found that metformin plus clomifene significantly improved clinical pregnancy rate compared with clomifene alone (8 RCTs: 182/486 [37%] with metformin plus clomifene *v* 144/490 [29%] with clomifene alone; OR 1.48, 95% CI 1.12 to 1.95). However, it found significant statistical heterogeneity (P = 0.0058) in this analysis. Subgroup analysis according to women's BMI found that metformin plus clomifene significantly increased clinical pregnancy rates compared with clomifene alone in obese women (BMI >30); however, it found no significant difference in the subgroup of women with BMI <30 (women with BMI >30: 5 RCTs: 110/319 [34%] with metformin plus clomifene *v* 78/324 [24%] with clomifene alone; OR 1.67, 95% CI 1.18 to 2.36; women with BMI <30: 3 RCTs: 72/167 [43%] with metformin plus clomifene *v* 66/166 [40%] with clomifene alone; OR 1.19, 95% CI 0.74 to 1.90) suggesting that the benefit of combination treatment may lie in the subgroup of obese women. The review found no significant difference between groups in live birth rate (4 RCTs: 88/373 [24%] with metformin plus clomifene *v* 86/379 [23%] with clomifene alone; OR 1.05, 95% CI 0.75 to 1.47). It also found no significant difference in live birth rates in the subgroup of obese women (3 RCTs: 67/262 [26%] with metformin plus clomifene *v* 55/265 [21%] with clomifene alone; OR 1.31, 95% CI 0.87 to 1.96). [19]

The second systematic review (3 RCTs [all of which were also identified by the first review], 720 people) found no significant difference between clomifene plus metformin versus clomifene alone for ovulation rate, pregnancy rate, and live birth rate, after six cycles (followed by 9-month extension to evaluate live birth in one RCT) (ovulation rate: 262/362 [72%] with clomifene alone *v* 271/358 [76%] with clomifene plus metformin; OR 0.84, 95% CI 0.60 to 1.18; pregnancy rate: 120/362 [33%] with clomifene alone *v* 132/358 [37%] with clomifene plus metformin; OR 0.85, 95% CI 0.62 to 1.15; live birth rate: 120/362 [33%] with clomifene alone *v* 132/358 [37%] with clomifene plus metformin; OR 0.99, 95% CI 0.70 to 1.40). [20]

The subsequent RCT (32 women with PCOS, mean BMI about 28) found no significant difference between clomifene plus metformin and clomifene plus placebo in ovulation rate after one to three cycles (10/16 [63%] with clomifene plus metformin *v* 6/16 [38%] with clomifene plus placebo; P = 0.1572). [21] However, the results of this study should be interpreted with caution, because of its small size, uncertainty about blinding in the study, and the method of randomisation was also not reported.

Metformin versus laparoscopic ovarian drilling (LOD):
See benefits of laparoscopic ovarian drilling, p 15 .

Metformin plus gonadotrophins versus LOD:
See benefits of gonadotrophins, p 11 .

Metformin plus gonadotrophins compared with gonadotrophins alone:
See benefits of gonadotrophins, p 11 .

Metformin plus in vitro fertilisation (IVF) versus IVF alone:
See benefits of IVF (ovulation disorders), p 18 .

Harms:

Metformin versus placebo:
The review found no significant difference between groups in miscarriage rate (4/40 [10%] with metformin *v* 3/11 [27%] with placebo; OR 0.30, 95% CI 0.06 to 1.59). [19] The review found that metformin significantly increased gastrointestinal disturbance, other than nausea and vomiting, compared with placebo (48/125 [38%] with metformin *v* 7/128 [5%] with placebo; OR 9.23, 95% CI 4.18 to 20.37). [19]

Metformin versus clomifene:
The first review found no significant difference between groups in miscarriage rate (13/60 [22%] with metformin *v* 22/85 [26%] with clomifene; OR 0.94, 95% CI 0.42 to 2.07). [19] The review is likely to have been underpowered to detect a clinically important difference in these outcomes because of low event rates in the RCTs identified.

The second review found no significant difference between groups for miscarriage rate/cycle started (13/296 [4%] with metformin *v* 20/298 [7%] with clomifene; OR [clomifene *v* metformin] 1.58, 95% CI 0.77 to 3.25) and with no significant difference in continuation rates for adverse events (7/296 [2.4%] with metformin *v* 5/298 [1.7%] with clomifene; OR [clomifene *v* metformin] 0.7, 95% CI 0.22 to 2.25). [20]

Metformin plus clomifene versus clomifene alone:
The first systematic review found no significant difference between groups in miscarriage rate or multiple pregnancy rate (miscarriage rate: 5 RCTs: 42/374 [11%] with clomifene plus metformin *v* 28/371 [8%] with clomifene alone; OR 1.48, 95% CI 0.90 to 2.43; multiple pregnancy rate: 4 RCTs: 3/334 [1%] with clomifene plus metformin *v* 6/331 [2%] with clomifene alone; OR 0.50, 95% CI 0.12 to 2.02). [19] It found significantly greater incidence of nausea and vomiting with clomifene plus metformin compared with clomifene alone (1 RCT: 72/209 [34%] with clomifene plus metformin *v* 28/209 [13%] with clomifene alone; OR 3.40, 95% CI 2.08 to 5.54). [19]

The second systematic review found no significant difference between metformin plus clomifene versus clomifene alone for miscarriage rate after six cycles (miscarriage rate: 26/362 [7%] with clomifene alone *v* 34/358 [9%] with clomifene plus metformin; OR 0.74, 95% CI 0.43 to 1.26). [20]

The subsequent RCT reported that almost all women treated with metformin reported gastrointestinal adverse effects, however, none of these women withdrew from the study (absolute numbers and statistical comparison between groups not reported). It found that one woman treated with clomifene plus metformin for three cycles was at high risk of ovarian hyperstimulation syndrome (OHSS), and treatment was discontinued.

Metformin versus LOD:
See harms of LOD, p 15 .

Metformin plus gonadotrophins versus LOD:
See harms of gonadotrophins, p 11 .

Metformin plus gonadotrophins compared with gonadotrophins alone:
See harms of gonadotrophins, p 11 .

Metformin plus IVF versus IVF alone:
See harms of IVF (ovulation disorders), p 18 .

Comment:

Metformin versus placebo:
None of the RCTs identified by the review assessed live birth rate or clinical pregnancy rate as a primary outcome measure for this comparison. [19]

Metformin plus clomifene versus clomifene alone:
Gastrointestinal symptoms are greater in women receiving metformin therapy. Any favourable effect of the combination therapy may potentially lie within the subgroup of women with a BMI >30, although there was ultimately no significant benefit with respect to live birth rates, and these women would be better advised to undergo lifestyle changes before fertility treatment. [19] [20]

OPTION GONADOTROPHINS FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Live birth rate
Gonadotrophins plus metformin compared with gonadotrophins alone We don't know whether gonadotrophins plus metformin are more effective than gonadotrophins alone at increasing live birth rate (moderate-quality evidence).

Compared with laparoscopic ovarian drilling (LOD) Gonadotrophins seem equally effective as LOD (with or without medical ovulation) at increasing live birth rates at 6 to 12 months in women with clomifene-resistant polycystic ovary syndrome (PCOS) (moderate-quality evidence).

Urinary human chorionic gonadotrophin (hCG) plus clomifene citrate versus clomifene citrate alone We don't know whether administering urinary hCG is more effective than no hCG at increasing live birth rate in anovulatory women being treated with clomifene (low-quality evidence).

Pregnancy rate
Urinary follicle-stimulating hormone (urofollitropin) compared with human menopausal gonadotrophin (hMG) We don't know whether urinary FSH or hMG are more effective at improving pregnancy rate in clomifene-resistant women with PCOS (low-quality evidence).

Gonadotrophins plus metformin compared with gonadotrophins alone Gonadotrophins plus metformin may be more effective than gonadotrophins alone at increasing pregnancy rate (low-quality evidence).

Compared with LOD Gonadotrophins seem equally effective as LOD (with or without medical ovulation) at increasing pregnancy rates at 6 to 12 months in women with clomifene-resistant PCOS (moderate-quality evidence).

Urinary human chorionic gonadotrophin (hCG) plus clomifene citrate versus clomifene citrate alone We don't know whether administering urinary hCG is more effective than no hCG at increasing pregnancy rate in anovulatory women being treated with clomifene (low-quality evidence).

Gonadotrophin-releasing hormone (GnRH) agonists plus gonadotrophins compared with gonadotrophins alone We don't know whether GnRH plus gonadotrophins are more effective than gonadotrophins alone at increasing pregnancy rates (low-quality evidence).

Ovulation rate
Urinary follicle-stimulating hormone (urofollitropin) compared with hMG We don't know whether urinary FSH or hMG is more effective at increasing ovulation rate in clomifene-resistant women with PCOS (low-quality evidence).

Urinary hCG plus clomifene citrate versus clomifene citrate alone We don't know whether administering urinary hCG is more effective than no hCG at increasing ovulation rate in anovulatory women being treated with clomifene (low-quality evidence).

GnRH agonists plus gonadotrophins compared with gonadotrophins alone We don't know whether GnRH agonists plus gonadotrophins are more effective than gonadotrophins alone at increasing ovulation rates (very low-quality evidence).

Compared with LOD Gonadotrophins seem equally effective as LOD at increasing ovulation rates at 6 months in women with clomifene-resistant PCOS (moderate-quality evidence).

Adverse effects
Gonadotrophins may be associated with a slight increase in risk of epithelial ovarian cancer compared with controls. Gonadotrophins have been associated with ovarian hyperstimulation syndrome and multiple pregnancies.

Note
We found no clinically important results from RCTs about the effects of gonadotrophins compared with no active treatment or clomifene (clomiphene).

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Gonadotrophins versus placebo or clomifene (clomiphene):
We found no RCTs meeting *Clinical Evidence* reporting criteria.

Urinary follicle-stimulating hormone (urofollitropin) versus human menopausal gonadotrophin (hMG):
We found one systematic review (search date not reported, 8 RCTs) comparing purified urinary FSH versus hMG for ovulation induction in clomifene-resistant women with polycystic ovary syndrome (PCOS). [24] It found no significant difference between FSH or hMG with or without GnRH agonist in ovulation rate or pregnancy rate (7 RCTs: ovulation rate: 216/312 [69%] with hMG *v*

232/315 [74%] with FSH; OR 0.75, 95% CI 0.52 to 1.07; pregnancy rate (per cycle): 31/312 [10%] with hMG *v* 35/315 [11%] with FSH; OR 0.89, 95% CI 0.53 to 1.49). [24] The review commented that none of the RCTs stated the method of randomisation, and only one RCT described blinding.

Gonadotrophins versus laparoscopic ovarian drilling:
See benefits of laparoscopic ovarian drilling, p 15 .

Gonadotrophins plus metformin versus gonadotrophins alone:
We found two systematic reviews (search dates 2005 [25] and 2007 [26]). The reviews identified RCTs in common; however, they applied different inclusion criteria and reported different analyses, so we have reported both here.

The first systematic review (search date 2005, 3 RCTs [2 RCTs also included in second review, 1 RCT excluded by the second review due to not reporting pregnancy rates before the crossover], 84 clomifene-resistant women with PCOS) compared metformin plus gonadotrophin ovulation induction versus gonadotrophin ovulation induction alone or plus placebo. It found no significant difference between metformin plus gondatrophins and gonadotrophins alone in pregnancy rate; however, this was higher with combined treatment (10/36 [28%] with metformin plus gonadotrophin *v* 4/41 [10%] with gonadotrophin alone; OR 3.46, 95% CI 0.98 to 12.2; P = 0.05). [25]

The second systematic review (search date 2007, 4 RCTs [2 RCTs also included in the first review]) compared metformin plus FSH versus FSH alone for ovulation induction using human chorionic gonadotrophin (hCG) trigger. [26] It found that metformin plus FSH significantly improved pregnancy rates compared with FSH alone (30/78 [38%] with metformin plus FSH *v* 17/76 [22%] with FSH alone; RR 1.72, 95% CI 1.07 to 2.78). It found no significant difference in live birth rate between metformin plus gonadotrophins and gonadotrophins alone; however, this was higher with metformin plus gonadotrophins (3 RCTs: 22/62 [35%] with metformin plus FSH *v* 13/60 [22%] with FSH alone; RR 1.64, 95% CI 0.95 to 2.85).

Urinary hCG plus clomifene citrate versus clomifene citrate alone:
We found one systematic review (search date 2007, 2 RCTs) comparing urinary hCG versus no treatment in women being treated with clomifene citrate. [27] The objective of the review was to determine the efficacy of administering an ovulation trigger compared with spontaneous ovulation in anovulatory women being treated with ovulation-inducing agents. The review found no significant difference between urinary hCG and no treatment in the primary outcome of live birth rate (26/155 [16.8%] with urinary hCG *v* 25/150 [16.7%] with no treatment; OR 0.98, 95% CI 0.52 to 1.83). It also found no significant difference between groups in ovulation rate or clinical pregnancy rate (ovulation rate: 133/155 [86%] with urinary hCG *v* 130/150 [87%] with no treatment; OR 0.95, 95% CI 0.49 to 1.83; clinical pregnancy rate: 28/155 [18%] with urinary hCG *v* 26/150 [17%] with no treatment; OR 1.02, 95% CI 0.56 to 1.88). The review reported that both RCTs were underpowered to detect differences in live birth rate, and one RCT was underpowered to detect differences in pregnancy rate and ovulation rate. One of the RCTs was single blinded, and the other RCT was open-label.

Gonadotrophin-releasing hormone (GnRH) agonists plus gonadotrophins versus gonadotrophins alone:
See benefits of GnRH agonists plus gonadotrophins for infertility caused by ovulation disorders, p 13 .

Harms:

Gonadotrophins versus placebo or clomifene:
We found no RCTs.

Urinary FSH (urofollitropin) versus hMG:
The review found a significantly higher rate of ovarian hyperstimulation syndrome (OHSS) with FSH compared with hMG with or without GnRH agonist (6 RCTs: OHSS/cycle: 12/199 [6%] with hMG *v* 27/197 [14%] with FSH; OR 0.33, 95% CI 0.16 to 0.65). [24] It found no significant difference between FSH and hMG in miscarriage rate or multiple pregnancy rate (4 RCTs: miscarriage rate/pregnancy: 7/22 [32%] with hMG *v* 10/25 [40%] with FSH; OR 0.85, 95% CI 0.24 to 2.96; multiple pregnancy rate/pregnancy: 2/22 [9%] with hMG *v* 4/28 [11%] with FSH; OR 0.62 CI 0.11 to 3.58). [24]

Gonadotrophins versus laparoscopic ovarian drilling:
See harms of laparoscopic ovarian drilling, p 15 .

Gonadotrophins plus metformin versus gonadotrophins alone:
The first review found that none of the RCTs reported on the incidence of OHSS. It gave no further information on adverse effects. [25]

The second review found that combined treatment significantly reduced multiple pregnancies compared with gonadotrophins alone (RR 0.26, 95% CI 0.07 to 0.96; absolute numbers not reported). It found no significant difference between groups in OHSS (RR 0.59, 95% CI 0.17 to 2.1; absolute numbers not reported). However, these results should be interpreted with caution because it is likely that there were too few cases to assess the effect of treatments on incidence of OHSS. [26]

Urinary hCG plus clomifene citrate versus clomifene citrate alone:
The review found no significant difference between groups in miscarriage rate (miscarriage rate: 3/28 [11%] with urinary hCG *v* 2/26 [8%] with no treatment; OR 1.18, 95% CI 0.18 to 7.66). [27]

GnRH agonists plus gonadotrophins versus gonadotrophins alone:
See harms of GnRH agonists plus gonadotrophins for infertility caused by ovulation disorders, p 13 .

Comment:

Clinical guide:
Despite not being placebo controlled, trials in the review of gonadotrophins provide evidence that treatment is effective. [24] Follitropin is not derived from human tissues, as it is derived from recombinant technology.

The guideline of the European Society of Reproduction and Embryology (ESHRE) consensus statement on treatment of infertility related to PCOS provides the following summary points for ovulation induction by gonadotrophins: 1) the recommended starting daily dose is 37.5 to 50 IU/day; 2) the starting period for stimulation should be at least 14 days for the first cycle as it is less likely to result in excessive stimulation; 3) when increasing doses of FSH, small incremental steps of 50% are less likely to result in excessive stimulation; 4) up to six cycles of stimulated ovulation should be performed; 5) it is essential to monitor the ovarian response; 6) cycle cancellation criteria should be established before commencement of therapy; 7) preventing all multiple pregnancies and OHSS is not possible at this time. [15]

Evidence derived from the reviews analysed suggests a potential benefit of concurrent administration of metformin with gonadotrophin ovulation induction at leading to monofollicular ovulation and reducing the number of multiple pregnancies in women with PCOS.

OPTION GONADOTROPHIN-RELEASING HORMONE (GNRH) AGONISTS PLUS GONADOTROPHINS FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Pregnancy rate
Compared with gonadotrophins alone We don't know whether gonadotrophin-releasing hormone (GnRH) agonists plus gonadotrophins are more effective than gonadotrophins alone at increasing pregnancy rates (low-quality evidence).

Ovulation rate
Compared with gonadotrophins alone We don't know whether GnRH agonists plus gonadotrophins are more effective than gonadotrophins alone at increasing ovulation rates (very low-quality evidence).

Note
Gonadotrophin agonists plus gonadotrophin combination treatments are associated with an increased risk of ovarian hyperstimulation syndrome and multiple pregnancy. We found no clinically important results from RCTs about the effects of GnRH agonists plus gonadotrophins compared with GnRH antagonists in women with ovulation disorders.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Gonadotrophin-releasing hormone (GnRH) agonists plus gonadotrophins versus gonadotrophins alone:
We found one systematic review (search date not reported, 4 RCTs) comparing gonadotrophin therapy with and without the concomitant use of GnRH agonist for ovulation induction in women with PCOS. [24] It found no significant difference in ovulation rate or pregnancy rate between gonadotrophin alone or gonadotrophin plus GnRH agonist (3 RCTs: ovulation rate: 62/93 [67%] with gonadotrophin plus GnRH agonist *v* 72/94 [77%] with gonadotrophin alone; OR 0.59, 95% CI 0.31 to 1.12; pregnancy rate 19/102 [19%] with gonadotrophin plus GnRH agonist *v* 15/109 [14%] with gonadotrophin alone; OR 1.43, 95% CI 0.67 to 3.04). [24] The review commented that none of the RCTs stated the method of randomisation or blinding.

Harms:

GnRH agonists plus gonadotrophins versus gonadotrophins alone:
The review found significantly higher rates of overstimulation per cycle with gonadotrophin plus GnRH agonist compared with gonadotrophin alone (2 RCTs: 24/90 [27%] with gonadotrophin plus GnRH agonist *v* 9/91 [10%] with gonadotrophin alone; OR 3.15, 95% CI 1.48 to 6.70). It found no

significant difference between groups in OHSS rate (3 RCTs: 9/93 [10%] with gonadotrophin plus GnRH agonist *v* 7/94 [7%] with gonadotrophin alone; OR 1.41, 95% CI 0.50 to 3.95). [24]

Comment:

Depot versus daily dose GnRH agonist:
We found one systematic review (search date 2004, 6 RCTs, 552 women) comparing depot GnRH agonist versus daily GnRH agonist. It found no significant difference between depot and daily GnRH agonist in clinical pregnancy rate per woman, ongoing pregnancy rate per cycle, multiple pregnancy rate, miscarriage rate, or incidence of OHSS. [29]

Clinical guide:
GnRH agonists plus gonadotrophin combination treatments are not widely used in ovulation induction treatment for ovulatory disorders because they do not improve pregnancy rates, and are associated with an increased risk of OHSS. [30] The Thesaloniki consensus statement [15] commented that the use of concomitant GnRH agonist administration led to a significantly higher hyperstimulation rate, and the associated risk of multiple pregnancies and the additional inconvenience and cost of concomitant GnRH agonist administration, in the absence of documented increases in pregnancy success, do not currently justify the routine use of GnRH agonists during ovulation induction with gonadotrophins in women with PCOS. GnRH agonists are most often used in conjunction with gonadotrophins to achieve pituitary downregulation and facilitate cycle control in ovarian stimulation during in vitro fertilisation (IVF) treatment.

OPTION GONADOTROPHIN-RELEASING HORMONE (GNRH) ANTAGONISTS FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Live birth rate
Compared with gonadotrophin-releasing hormone (GnRH) agonists We don't know how GnRH antagonists or GnRH agonists compare with each other at increasing live birth rates in women with polycystic ovary syndrome (PCOS) (moderate-quality evidence).

Pregnancy rate
Compared with GnRH agonists We don't know how GnRH antagonists or GnRH agonists compare with each other at increasing pregnancy rates in women with PCOS (low-quality evidence).

Note
We found no clinically important results from RCTs about the effects of GnRH antagonists compared with no active treatment.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Gonadotrophin-releasing hormone (GnRH) antagonists versus placebo:
We found no systematic review or RCTs in women with ovulatory disorders.

GnRH antagonists versus GnRH agonists in an IVF cycle:
We found one systematic review (search date 2006, 4 RCTs [one of which was published in abstract form], 305 women with PCOS) examining the use of GnRH antagonist for ovarian stimulation for in vitro fertilisation (IVF). [31] All studies involved pretreatment with oral contraceptive pill, and used the long agonist protocol. It found no significant difference between groups in pregnancy rate (4 RCTs: 56/151 [37%] with antagonist *v* 64/154 [42%] with agonist; OR 0.82, 95% CI 0.51 to 1.32; P = 0.42). The review reported that the method of randomisation was not reported in two of the included RCTs.

We found another systematic review (search date 2005), which identified two RCTs, which were also identified by the first systematic review. However, this review reported on the outcome of live birth rate. It found no significant difference between groups in live birth rate (37/100 [37%] with antagonist *v* 41/104 [39%] with agonist; OR 0.90, 95% CI 0.51 to 1.58). [32]

GnRH antagonists versus other treatments:
We found no systematic review or RCTs.

Harms:

GnRH antagonists versus placebo:
We found no RCTs.

GnRH antagonists versus GnRH agonists in an IVF cycle:
The first systematic review found that there were no cases of severe ovarian hyperstimulation syndrome (OHSS). [31] It found no significant difference between groups in the incidence of OHSS (grades 1 to 2) (2 RCTs: 5/100 [5%] with antagonist *v* 7/104 [7%] with agonist; OR 0.73, 95% CI 0.22 to 2.38). However, results should be interpreted with caution because the analysis may have

been underpowered because of the small number of cases. The review commented that in women at risk of OHSS, GnRH-agonist triggering seems to be associated with a reduction in the incidence of mild and moderate OHSS. [31]

The second systematic review did not report on the incidence of OHSS in the subgroup of women with PCOS. It found that in a general population, GnRH antagonist was associated with a significantly reduced incidence of OHSS requiring admission to hospital compared with GnRH agonist (7 RCTs: OR 0.46, 95% CI 0.26 to 0.82; P = 0.01; absolute numbers not reported). [32]

GnRH antagonists versus other treatments:
We found no RCTs.

Comment:

Clinical guide:
Women with PCOS are at a substantial risk of OHSS in an IVF cycle. The systematic review suggests that the use of an antagonist may reduce the incidence of OHSS [32] in the general population, and potentially this treatment should be considered for women with PCOS.

OPTION LAPAROSCOPIC OVARIAN DRILLING (LOD) FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Live birth rate
Compared with gonadotrophins Laparoscopic ovarian drilling (LOD) (with or without medical ovulation) seems equally effective as gonadotrophins at increasing live birth rates at 6 to 12 months in women with clomifene-resistant polycystic ovary syndrome (PCOS) (moderate-quality evidence).

Compared with metformin LOD seems less effective than metformin at increasing live birth rates in women with clomifene-resistant PCOS (moderate-quality evidence).

LOD plus metformin compared with LOD alone We don't know whether LOD followed by metformin or LOD alone is more effective at increasing live birth rates (low-quality evidence).

Compared with clomifene We don't know whether initial treatment with clomifene or LOD is more effective at increasing live birth rates in anovulatory women (low-quality evidence).

Pregnancy rate
Compared with metformin We don't know whether LOD or metformin is more effective at increasing pregnancy rates in women with clomifene-resistant PCOS (low-quality evidence).

Compared with gonadotrophins LOD (with or without medical ovulation) seems equally effective as gonadotrophins at increasing pregnancy rates at 6 to 12 months in women with clomifene-resistant PCOS (moderate-quality evidence).

LOD plus metformin compared with LOD alone We don't know whether LOD followed by metformin or LOD alone is more effective at increasing pregnancy rates (low-quality evidence).

Compared with clomifene We don't know whether initial treatment with clomifene or LOD is more effective at increasing pregnancy rates in anovulatory women (low-quality evidence).

Ovulation rate
Compared with clomifene We don't know whether clomifene or LOD is more effective at increasing ovulation rates in anovulatory women (moderate-quality evidence).

Compared with metformin We don't know whether LOD or metformin is more effective at increasing ovulation rates in women with clomifene-resistant PCOS (very low-quality evidence).

Compared with gonadotrophins LOD seems equally effective as gonadotrophins at increasing ovulation rates at 6 months in women with clomifene-resistant PCOS (moderate-quality evidence).

Note
LOD has been associated with lower risks of multiple pregnancy compared with gonadotrophins. We found no direct information from RCTs about whether LOD is better than no active treatment.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Laparoscopic ovarian drilling (LOD) versus no treatment:
We found no RCTs.

LOD versus gonadotrophins:
We found one systematic review (search date 2007, 5 RCTs), which compared LOD with or without ovarian stimulation versus gonadotrophins alone in women with anovulatory clomifene (clomiphene)-resistant PCOS. [28] It found no significant difference in live birth rates between ovarian drilling and gonadotrophins (3 cycles) at 6 months' follow-up (1 RCT: 4/29 [14%] with ovarian drilling *v* 4/21 [19%] with gonadotrophins; OR 0.68, 95% CI 0.15 to 3.10). It also found no significant difference in live birth rates after ovarian drilling with or without medical ovulation induction versus gonadotrophins (6 cycles) at 12 months' follow-up (1 RCT: 52/83 [63%] with ovarian drilling with or without medical ovulation induction *v* 51/85 [60%] with gonadotrophins alone; OR 1.12, 95% CI 0.60 to 2.08). The review found no significant difference in pregnancy rates between LOD and gonadotrophins (3 cycles) at 6 months' follow-up (1 RCT: 5/29 [17%] with LOD *v* 5/21 [24%] with gonadotrophins; OR 0.67, 95% CI 0.17 to 2.68). It also found no significant difference between ovarian drilling with or without medical ovulation and gonadotrophins (6 cycles) at 12 months' follow-up (3 RCTs: 75/128 [59%] with LOD *v* 71/126 [56%] with gonadotrophins; OR 1.15, 95% CI 0.69 to 1.93). [28] It found no significant difference in ovulation rate between LOD and gonadotrophins (3 cycles) at 6 months' follow-up (1 RCT: 15/29 [52%] with LOD *v* 13/21 [62%] with gonadotrophins; OR 0.66, 95% CI 0.21 to 2.07).

LOD versus metformin:
We found one systematic review (search date 2007), which identified one RCT comparing LOD versus metformin in clomifene-resistant women with PCOS. [26] It found no significant difference between groups in clinical pregnancy rate after six cycles of treatment (39/54 [72%] with metformin *v* 31/55 [56%] with LOD; RR 1.28, 95% CI 0.96 to 1.7). It found that metformin significantly increased live birth rate compared with LOD (32/54 [59%] with metformin *v* 20/55 [36%] with LOD; RR 1.63, 95% CI 1.08 to 2.46). [26]

We found one additional RCT (161 women with clomifene-resistant PCOS) comparing laparoscopic drilling versus metformin. If spontaneous ovulation or pregnancy was not achieved within 3 months after treatment, clomifene was added for both groups. The RCT found no significant difference between laparoscopic drilling and metformin in pregnancy or ovulation rates (follow-up time not reported) (pregnancy: 58/97 [60%] with laparoscopic drilling *v* 41/64 [64%] with metformin; ovulation rate: 81/97 [84%] with laparoscopic drilling *v* 51/64 [80%] with metformin; results reported as not significant for both outcomes; P values not reported). [33]

LOD versus LOD plus metformin:
We found one systematic review (search date 2007), which identified one small RCT comparing LOD versus LOD plus metformin. It found no significant difference between groups in pregnancy rates or live birth rates (pregnancy rates: 9/21 [4%] with LOD plus metformin *v* 4/21 [2%] with LOD; RR 2.25, 95% CI 0.82 to 6.18; live birth rates: 5/21 [2%] with LOD plus metformin *v* 4/21 [2%] with LOD; RR 1.25, 95% CI 0.39 to 4.02). [26] The review commented that the method of randomisation used in the RCT was not clear and the RCT was unblinded.

LOD versus clomifene:
See benefits of clomifene, p 4 .

Harms:

Adverse effects associated with LOD include the risks of general anaesthesia, a low risk of postoperative adhesion formation, [34] and pelvic infection. [35] We found no evidence to support the suggestion that laparoscopic drilling increases the long-term risk of premature ovarian failure. Although markers of ovarian reserve are reduced after surgery they still remain higher than in similar women without PCOS. [36] Laparoscopic drilling is thought not to increase the risk of multiple pregnancies as it usually induces spontaneous ovulation, by contrast with the multifollicular ovulation that may be induced by the use of gonadotrophins. [15]

LOD versus gonadotrophins:
The systematic review found no significant difference in miscarriage rates between ovarian drilling and gonadotrophins (4 RCTs: 12/88 [14%] with ovarian drilling *v* 14/85 [16%] with gonadotrophins; OR 0.81, 95% CI 0.36 to 1.86). It found significantly lower incidence of multiple pregnancy with ovarian drilling with or without medical ovulation and gonadotrophins only where there was a direct comparison between these groups (5 RCTs: multiple pregnancy rate/ongoing pregnancy: 1/84 [1%] with ovarian drilling *v* 14/82 [17%] with gonadotrophins; OR 0.13, 95% CI 0.03 to 0.59). [28]

LOD versus metformin:
The review reported that no multiple pregnancies were observed in the RCT, but gave no further information on adverse effects. [26]

We found one RCT, [33] which was excluded from the systematic review. [26] This RCT found no significant difference between LOD and metformin in the rates of multiple pregnancy, ovarian hy-

perstimulation syndrome (OHSS), or ectopic pregnancy (multiple pregnancy: 4/58 [7%] with ovarian drilling *v* 2/41 [5%] with metformin; OHSS: 2/58 [3%] with ovarian drilling *v* 1/41 [2%] with metformin; ectopic pregnancy: 3/58 [5%] with ovarian drilling *v* 1/41 [2%] with metformin; all outcomes reported as not significant; P values not reported). [33]

LOD versus laparoscopic ovarian drilling plus metformin:
The review gave no information on adverse effects.

LOD versus clomifene:
See harms of clomifene, p 4 .

Comment:

Clinical guide:
The trials of LOD included women who were not ovulating and, therefore, provide some evidence that treatment is effective despite the lack of placebo controls. [28]

OPTION PULSATILE GONADOTROPHIN-RELEASING HORMONE (GNRH) FOR INFERTILITY CAUSED BY OVULATION DISORDERS

Pregnancy rate
Compared with clomifene We don't know whether pulsatile gonadotrophin-releasing hormone (GnRH) plus GnRH agonist or clomifene are more effective at increasing pregnancy rates in women with polycystic ovary syndrome (PCOS) (low-quality evidence).

Ovulation rate
Compared with clomifene We don't know whether pulsatile GnRH plus GnRH agonist or clomifene are more effective at increasing ovulation rates in women with PCOS (low-quality evidence).

Note
We found no clinically important results from RCTs about the effects of pulsatile GnRH compared with human menopausal gonadotrophin, about pulsatile GnRH plus follicle-stimulating hormone (FSH) compared with FSH alone, or about pulsatile GnRH plus GnRH agonist compared with pulsatile GnRH alone.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Pulsatile gonadotrophin-releasing hormone (GnRH) plus GnRH agonist versus clomifene (clomiphene):
We found one systematic review (search date 2003, 1 RCT, 28 women with polycystic ovary syndrome [PCOS]). [37] The RCT compared pulsatile gonadotrophin-releasing hormone (GnRH; 10–20 µg intravenously [iv] every 90 minutes) immediately after pretreatment with a GnRH agonist (400 µg intranasally for at least 3 weeks) versus clomifene (50 mg started on cycle day 3–7). It found no significant difference between treatments in pregnancy rate per woman or ovulation rate per cycle (pregnancy: 4/16 [25%] with pulsatile GnRH after GnRH agonist *v* 4/12 [33%] with clomifene; OR 0.67, 95% CI 0.13 to 3.43; ovulation: 19/40 [47%] with pulsatile GnRH after GnRH agonist *v* 15/25 [60%] with clomifene; OR 0.61, 95% CI 0.23 to 1.65; see comment below). The review reported that the RCT had methodological weaknesses including no blinding and inadequate allocation concealment (allocation by oral communication). [37] The RCT may have been too small to detect a clinically important difference between treatments.

Pulsatile GnRH versus other treatments:
The systematic review (search date 2003) identified three RCTs, none of which met *Clinical Evidence* inclusion criteria because of small sample sizes. The first RCT (9 women with clomifene-resistant PCOS) compared pulsatile GnRH versus human menopausal gonadotrophin (hMG), the second RCT (8 clomifene-resistant women with oligomenorrhoea and infertility for at least 3 years) compared pulsatile gonadotrophin plus FSH versus FSH alone and the third RCT compared pulsatile GnRH after pretreatment with a GnRH agonist versus pulsatile GnRH alone. [37]

Harms:

Pulsatile GnRH plus GnRH agonist versus clomifene:
The RCT identified by the systematic review found no cases of ovarian hyperstimulation syndrome (OHSS) or multiple pregnancy per woman in either treatment group, see comment below. [37]

Pulsatile GnRH versus other treatments:
The RCTs identified by the systematic review did not meet *Clinical Evidence* inclusion criteria. [37] One retrospective analysis (229 cycles in 71 women) compared pulsatile GnRH versus gonadotrophins alone and found no significant difference in multiple pregnancy rates after six cycles. [37] However, 75% of the multiple pregnancies in the gonadotrophin group were triplets or higher order multiple pregnancies, whereas all multiple pregnancies in the GnRH group were twins.

Comment: Case series (256 anovulatory women with hypogonadotrophic hypogonadism having 1043 treatment cycles) found cumulative pregnancy rates of 59% to 73% at 6 months and 81% to 92% at 12 months. [38] [39] [40] Only one series reported the live birth rate; this was 65% after 12 treatment cycles. [40]

Clinical guide:
Pulsatile GnRH is used in women with anovulation caused by low serum gonadotrophins and oestrogen concentrations (hypogonadotrophic hypogonadism); however, this treatment is rarely used nowadays and there is a paucity of recent publications in this area. Hypogonadotrophic hypogonadism is a well-defined condition and so evidence from case series should be generalisable to most affected women.

OPTION IN VITRO FERTILISATION (IVF) IN OVULATION DISORDERS

Live birth rate
Metformin plus in vitro fertilisation (IVF) compared with IVF alone Adding metformin to IVF or intracytoplasmic sperm injection (ICSI) seems no more effective than IVF or ICSI alone at increasing live birth rates (moderate-quality evidence).

Pregnancy rate
Metformin plus IVF compared with IVF alone We don't know whether adding metformin to IVF/ICSI is more effective at increasing pregnancy rates (low-quality evidence).

Note
We found no direct information from RCTs about whether IVF is better than no active treatment in women with ovulation disorders; however, the general body of opinion is that it is a successful treatment.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

In vitro fertilisation (IVF) versus no treatment:
We found no systematic review or RCTs comparing in vitro fertilisation (IVF) versus no treatment in women with ovulation disorders. However, RCTs are unlikely to be conducted (see comment).

Metformin plus IVF versus IVF alone:
We found one systematic review (search date 2008, 6 RCTs) comparing metformin as an adjunct to either IVF or intracytoplasmic sperm injection (ICSI) cycle versus no treatment/placebo with IVF/ICSI in women with polycystic ovary syndrome (PCOS). [23] One RCT started metformin on the first day of ovarian hyperstimulation with FSH, the other studies used metformin before and during ovarian hyperstimulation for IVF/ICSI. One of the identified RCTs additionally used an assisted hatching procedure using laser in the following cases: age of woman >35 years, thick zona pellucida, abnormally shaped zona, or where excessive embryo fragmentation or slowly developing embryos were noted. The review considered that this procedure was substantively different compared with that used in the other trials, and so it pooled data on outcomes from all relevant RCTs, and also excluded this study to pool data separately from studies where no assisted hatching procedure was used. We have presented both these analyses for the outcomes of live birth rate and clinical pregnancy rate.

The review found no significant difference in live birth rate between adding metformin or adding placebo/no treatment to IVF/ICSI, in all trials or in the subgroup of trials that did not use assisted hatching procedure (all trials: 3 RCTs: 39/136 [29%] with metformin *v* 33/136 [24%] with placebo/no treatment; OR [placebo *v* metformin] 0.77, 95% CI 0.27 to 2.18; trials without assisted hatching procedure: 2 RCTs: 29/83 [35%] with metformin *v* 17/81 [21%] with placebo/no treatment; OR [placebo *v* metformin] 0.49, 95% CI 0.17 to 1.38). It found no significant difference between groups in clinical pregnancy rate in all trials (all trials: 5 RCTs: 71/216 [33%] with metformin *v* 56/210 [27%] with placebo/no treatment; OR [placebo *v* metformin] 0.71, 95% CI 0.39 to 1.28). However, it found that metformin significantly increased the clinical pregnancy rate compared with placebo or no treatment group in trials in women who had no assisted hatching procedure (trials without assisted hatching procedure: 4 RCTs: 55/163 [34%] with metformin *v* 34/155 [22%] with placebo or no treatment; OR [placebo *v* metformin] 0.53, 95% CI 0.32 to 0.89). [23] It found no reduction in the number of oocytes retrieved.

IVF plus gonadotrophin-releasing hormone (GnRH) antagonist in controlled ovarian hyperstimulation versus IVF plus GnRH agonist:
See benefits of GnRH antagonist, p 14 .

Harms:

IVF versus no treatment:
We found no RCTs (see harms of IVF under treatments for tubal infertility, p 25).

Metformin plus IVF versus IVF alone:
The review found no significant difference between groups in miscarriage rate per woman (4 RCTs: 16/145 [11%] with metformin *v* 18/144 [13%] with placebo or no treatment; OR 0.84, 95% CI 0.40 to 1.75). [23] However, it should be noted that metformin was not continued during pregnancy in any of the studies. The review found a significantly reduced rate of ovarian hyperstimulation syndrome (OHSS) associated with adding metformin compared with adding placebo/no treatment to IVF/ICSI (5 RCTs: 13/227 [6%] with metformin *v* 47/222 [21%] with placebo or no treatment; OR 0.27, 95% CI 0.16 to 0.47). However, it found a significantly higher incidence of adverse effects with adding metformin compared with adding placebo/no treatment (3 RCTs: 46/135 [34%] with metformin *v* 13/136 [10%] with placebo or no treatment; OR [placebo *v* metformin] 0.22, 95% CI 0.05 to 0.99). [23]

IVF plus GnRH antagonist in controlled ovarian hyperstimulation versus IVF plus GnRH agonist:
See harms of GnRH antagonist, p 14 .

Comment:

RCTs comparing IVF versus no treatment are unlikely to be conducted. The European Society of Reproduction and Embryology (ESHRE) consensus on infertility treatment related to PCOS recommendation has stated that anovulation is not an indication for IVF. [15]

We found one systematic review (search date 2004) examining the outcomes of conventional IVF in women with PCOS. [41] The review identified no RCTs, but it pooled data from observational studies comparing IVF outcomes in women with PCOS versus primarily age-matched controls without PCOS (8 retrospective studies, 1 prospective study; 458 women with PCOS [793 cycles] and 694 matched controls [1116 cycles]). It found that women with PCOS had a significantly reduced chance of reaching oocyte retrieval in an IVF cycle (cycle cancellation) compared with matched controls (OR 0.5, 95% CI 0.2 to 1.0). However, it found no significant difference in the chance of embryo transfer per oocyte retrieval (OR 0.7, 95% CI 0.4 to 1.3). It found that significantly more oocytes were obtained per retrieval in women with PCOS (absolute results not reported, WMD 3.4, 95% CI 1.7 to 5.1), but it found no significant difference between groups in the clinical pregnancy rates per started cycle (OR 1.0, 95% CI 0.8 to 1.3). It found that the incidence of OHSS was rarely reported in identified studies. It found that women with PCOS and controls undergoing IVF achieved similar pregnancy and live birth rates per cycle. [41]

Clinical guide:
These results suggest that IVF is as successful in anovulatory women as it is in normo-ovulatory women although it is expected that these women are at an increased risk of OHSS. It is unlikely that pregnancy rates between women with ovulation disorders and normo-ovulatory women will differ as anovulation does not affect uterine receptivity for implantation. Once ovulation is achieved, the chance of pregnancy should not differ. The use of metformin should be strongly encouraged as an adjunct to an IVF/ICSI cycle as it reduces the incidence of OHSS without an apparent influence on live birth rates, although with an increased incidence of adverse effects.

OPTION INTRAUTERINE INSEMINATION ALONE, OR COMBINED WITH GONADOTROPHINS OR CLOMIFENE FOR INFERTILITY CAUSED BY OVULATION DISORDERS

We found no clinically important results from RCTs about the effects of intrauterine insemination (IUI) alone, or combined with gonadotrophins or clomifene in women with ovulation disorders.

Note
The use of IUI for women with ovulatory disorder is not standard.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Intrauterine insemination (IUI) alone or plus gonadotrophins or clomifene versus placebo/no treatment:
We found no systematic review or RCTs.

IUI alone or plus gonadotrophins or clomifene versus each other:
We found one systematic review (search date 2006) comparing human chorionic gonadotrophin (hCG) versus conservative urinary luteinising monitoring for timing of IUI. The review reported a subgroup analysis in women with ovulatory disorder. However, the data were primarily derived from observational studies (2 retrospective observational studies [199 women], 1 crossover study [37 women]). [42] For further information on results from this meta-analysis, see comment below.

Harms:

IUI alone or plus gonadotrophins or clomifene versus placebo/no treatment:
We found no RCTs.

IUI alone or plus gonadotrophins or clomifene versus each other:
The review gave no information on adverse effects of treatments in the subgroup of women with ovulation disorders. [42]

Comment:

IUI alone or plus gonadotrophins or clomifene versus each other:
The systematic review found no significant difference in pregnancy rates between IUI plus hCG plus clomifene versus IUI plus clomifene plus urinary luteinising hormone monitoring. However, pregnancy rate was higher with IUI plus hCG plus clomifene (18/112 [16%] with IUI plus hCG plus clomifene *v* 10/124 [8%] with IUI plus clomifene plus urinary luteinising hormone monitoring; OR 2.00, 95% CI 0.84 to 4.77). [42]

Clinical guide:
Guidelines from the European Society of Reproduction and Embryology and the American Society of Reproductive Medicine state that for pure ovulatory disorder, the addition of IUI to the ovulation induction protocol is not indicated unless there is an associated male factor or after several unsuccessful attempts. [15]

It is interesting that there is a lack of evidence on the effects of IUI plus controlled ovarian stimulation in the treatment of infertility caused by ovulation disorders. Consensus considers IUI plus controlled ovarian stimulation as effective in the management of infertility owing to cervical hostility, unexplained infertility, and mild male factor infertility.

OPTION GONADOTROPHIN PRIMING OF OOCYTES BEFORE IN VITRO MATURATION

Pregnancy rate
Compared with no priming We don't know whether gonadotrophin priming (with recombinant follicle-stimulating hormone [follitropin], human chorionic gonadotrophin [hCG], or follitropin plus hCG) of immature oocytes before in vitro maturation increases pregnancy rates compared with no priming in women with ovulation disorders (very low-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Follicle-stimulating hormone (follitropin) for priming versus no priming:
We found one RCT (28 women with polycystic ovary syndrome (PCOS) who had not responded to three or more previous in vitro fertilisation [IVF] treatments), which compared priming with follitropin (150 IU for 3 days, initiated on day 3 after menstruation, 24 cycles) before harvesting of immature oocytes versus no priming (12 cycles). [43] It found that priming with follitropin significantly increased pregnancy rates compared with no priming (0/12 [0%] with no priming *v* 7/24 [29%] with follitropin; P <0.05). Pregnancy resulted in a live birth in 3/24 (12%) women who received follitropin (P value not reported). [43]

One systematic review (search date 2007) comparing in vitro maturation versus conventional IVF or intracytoplasmic sperm injection (ISCI) (see comment) also commented on this RCT; however, it did not specifically search for or include studies on this comparison. [44]

Human chorionic gonadotrophin (hCG) for priming versus no priming:
We found no RCTs satisfying *Clinical Evidence* inclusion criteria that compared priming with hCG versus no priming.

FSH (follitropin) plus hCG for priming versus hCG alone for priming:
We found one RCT (60 women with PCOS, 68 cycles assessed) comparing priming with follitropin (75 IU for 6 days; 35 cycles) plus hCG (10,000 IU, 36 hours before oocyte retrieval) versus priming with hCG alone (33 cycles). [45] It found no significant difference in pregnancy rates between priming with follitropin plus hCG and priming with hCG alone (31% with follitropin plus hCG *v* 36% with hCG alone; P = 0.799).

Gonadotrophin priming of oocytes before in vitro maturation versus conventional IVF:
We found one systematic review (search date 2007). The review found no RCTs comparing in vitro maturation (including in vitro maturation with gonadotrophins or gonadotrophin priming before in vitro maturation) versus conventional IVF. For comment and information from observational studies on the benefits of in vitro maturation versus conventional IVF or ICSI, see comment. [44]

Harms:

FSH (follitropin) for priming versus no priming:
The RCTs gave no information on adverse effects. [43]

Human chorionic gonadotrophin for priming versus no priming:
We found no RCTs satisfying *Clinical Evidence* inclusion criteria.

FSH (follitropin) plus hCG for priming versus hCG alone for priming:
The RCTs gave no information on adverse effects. [45]

Gonadotrophin priming of oocytes before in vitro maturation versus conventional IVF:
We found no RCTs. For comment and information from observational studies on the adverse effects of in vitro maturation versus conventional IVF or ICSI, see comment.

Comment:

Clinical guide:
There is little information about the maturational capacity of immature oocytes derived from women with ovulation disorders who have been primed with gonadotrophins. In vitro maturation of oocytes may reduce the risk of ovarian hyperstimulation and may simplify treatment of women with ovulation disorders. However, the maturation rate of immature oocytes retrieved from women with ovulation disorders, particularly PCOS, is lower than that of those retrieved from women with normal menstrual cycles. [46] More RCTs are needed to reach a firm conclusion.

The systematic review, described in the benefits section, reported that it found observational evidence to support the use of in vitro maturation as a promising alternative to conventional IVF or ICSI in women with PCOS, especially regarding the prevention of ovarian hyperstimulation syndrome (OHSS). [44] It noted the following from observational studies with regard to in vitro maturation: a high maturation rate of oocytes (up to 80%), fertilisation rates (ranging from 10% to 77%), live birth rates (up to 33% per cycle), and similar frequency of chromosomal abnormalities and outcomes compared with women undergoing conventional assisted reproduction techniques. [44] The review commented that rates of miscarriage, ectopic pregnancy, and late fetal loss were similar with in vitro maturation and IVF or ICSI in women with PCOS. [44]

QUESTION What are the effects of treatments for tubal infertility?

OPTION SELECTIVE SALPINGOGRAPHY PLUS TUBAL CATHETERISATION FOR TUBAL INFERTILITY

We found no clinically important results from RCTs about the effects of selective salpingography plus tubal catheterisation compared with no active treatment in women with tubal infertility.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits: We found no systematic review or RCTs. For information on effects of selective salpingography plus tubal catheterisation from observational studies, see comment.

Harms: We found no RCTs. For information on adverse effects of selective salpingography plus tubal catheterisation from observational studies, see comment.

Comment: One systematic review (search date not reported) combined data from 10 cohort and other observational studies of selective salpingography and tubal cannulation (482 women), and four observational studies of hysteroscopic cannulation for proximal tubal blockage (133 women). [48] Crude analysis of aggregated data suggests that hysteroscopic cannulation was associated with a higher pregnancy rate compared with selective salpingography and tubal catheterisation (65/133 [49%] with hysteroscopic cannulation *v* 103/482 [21%] with selective salpingography and tubal catheterisation). Heterogeneity analysis revealed two distinct prognostic subgroups within the selective salpingography and tubal catheterisation cohort — one with low (12%) and the other with high (39%) pregnancy rates. None of the observational studies included an untreated group, so it is not possible to estimate the treatment-related pregnancy rate over and above the spontaneous pregnancy rate. Tubal patency and pregnancy without treatment have been reported in women diagnosed with bilateral proximal tube obstruction. [49]

Observational studies found that ectopic pregnancy occurred in 3% to 9% of women having selective salpingography and tubal catheterisation and that tubal perforation, which does not seem to be clinically important, occurred in 2%. [48] [50]

OPTION TUBAL FLUSHING WITH OIL SOLUBLE MEDIA FOR TUBAL INFERTILITY

Pregnancy rate
Compared with water-based media We don't know whether tubal flushing with oil-based media or tubal flushing with water-based media are more effective at increasing pregnancy rates in women with infertility because of tubal infertility (low-quality evidence).

Note

We found no clinically important results from RCTs about the effects of tubal flushing compared with no intervention solely in women with tubal infertility.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Tubal flushing with oil soluble media versus no intervention:
We found no systematic review or RCTs solely in women with tubal infertility. We found one systematic review (search date 2007), which compared tubal flushing with oil soluble media versus no intervention in women with various causes of infertility. [51] For data on pregnancy rate and live birth rate in women with infertility of any cause from this review, see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Tubal flushing with oil soluble media versus tubal flushing with water soluble media:
We found one systematic review (search date 2007), which compared tubal flushing with oil soluble media versus water soluble media. [51] The review carried out a subgroup analysis of women with tubal infertility. It found no significant difference in pregnancy rate between flushing with oil soluble media and flushing with water soluble media (subgroup analysis from 1 RCT: 2/12 [17%] with oil soluble media *v* 3/19 [16%] with water soluble media; Peto OR 1.06, 95% CI 0.15 to 7.36). [51] For information on tubal flushing in women with any cause of infertility, see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Tubal flushing with oil soluble plus water soluble contrast media versus tubal flushing with water soluble media only:
We found one systematic review (search date 2007, 5 RCTs, women with infertility of any cause who had been attempting conception for >12 months). The review carried out a subgroup analysis of pregnancy rate in women with tubal infertility. However, this subgroup of women (13 women) was too small to make any reliable conclusions. [51] For data on pregnancy rate and live birth rate in women with infertility of any cause from this review, see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Harms:

Tubal flushing with oil soluble media versus no intervention:
We found no RCTs solely in women with tubal fertility. For information on adverse effects of tubal flushing in women with any cause of infertility, see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Tubal flushing with oil soluble media versus tubal flushing with water soluble media:
The systematic review did not report adverse effects separately for women with tubal fertility. For information on adverse effects in women with infertility of any cause, see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Tubal flushing with oil soluble plus water soluble contrast media versus tubal flushing with water soluble media only:
The systematic review did not report adverse effects separately for women with tubal fertility. For information on adverse effects in women with infertility of any cause see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Comment: None.

OPTION TUBAL FLUSHING WITH WATER SOLUBLE MEDIA FOR TUBAL INFERTILITY

Pregnancy rate
Compared with oil-based media We don't know whether tubal flushing with water-based media or tubal flushing with oil-based media is more effective at increasing pregnancy rates in women with infertility because of tubal infertility (low-quality evidence).

Note
We found no clinically important results from RCTs about tubal flushing solely in women with tubal infertility.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Water soluble media versus no intervention:
We found no systematic review or RCTs solely in women with tubal infertility. For information on tubal flushing in women with any cause of infertility, see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Tubal flushing with water soluble versus tubal flushing with oil soluble media:
See benefits of tubal flushing with oil soluble media, p 21 .

Tubal flushing with oil soluble contrast media plus water soluble media versus water soluble media:
See benefits of tubal flushing with oil soluble media, p 21 .

Harms:

Water soluble media versus no intervention:
We found no systematic review or RCTs solely in women with tubal infertility. For information on tubal flushing in women with any cause of infertility, see comment in option on flushing in women with infertility of any cause, in question on endometriosis, p 30 .

Tubal flushing with water soluble versus tubal flushing with oil soluble media:
See harms of tubal flushing with oil soluble media, p 21 .

Tubal flushing with oil soluble contrast media plus water soluble media versus water soluble media:
See harms of tubal flushing with oil soluble media, p 21 .

Comment:

Clinical guide:
The clinical impression of an enhanced pregnancy rate after performing HyCoSy could not be confirmed. Tubal investigation with sonography using water-soluble contrast has a function as a diagnostic procedure but not in terms of increasing pregnancy rates in subfertile patients. [52]

OPTION TUBAL SURGERY FOR TUBAL INFERTILITY

Live birth rate
Compared with no treatment or medical treatment Tubal surgery seems more effective than no treatment or medical treatment at increasing live birth rates in women with hydrosalpinges who are undergoing in vitro fertilisation (IVF) (moderate-quality evidence).

Pregnancy rate
Compared with no treatment or medical treatment Tubal surgery may be more effective than no treatment or medical treatment at increasing pregnancy rates in women with hydrosalpinges who are undergoing IVF (low-quality evidence).

CO_2 laser adhesiolysis compared with diathermy adhesiolysis CO_2 laser adhesiolysis is as effective as diathermy adhesiolysis at increasing pregnancy rates (moderate-quality evidence).

Note
We found no clinically important results from RCTs about the effects of tubal surgery compared with IVF in women with tubal infertility.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Tubal surgery versus no treatment or medical treatment:
We found two systematic reviews (search dates 2005 [53] and 2007 [54]), which found no RCTs comparing infertility surgery versus no treatment or alternative treatments.

We found one systematic review (search date 2004, 3 RCTs, 295 women with hydrosalpinges having in vitro fertilisation [IVF] treatment). [55] The review found that tubal surgery before IVF significantly increased pregnancy and live birth rates compared with no treatment or medical treatment before IVF (pregnancy rate: 60/161 [37%] with surgery *v* 34/134 [25%] with no treatment or medical treatment; OR 1.75, 95% CI 1.07 to 2.86; live birth rate: 48/161 [30%] with surgery *v* 22/134 [16%] with no treatment or medical treatment; OR 2.13, 95% CI 1.24 to 3.65). [55] A variety of different surgical techniques were used in the included RCTs; however, laparoscopic unilateral or bilateral salpingectomy were the most common (numerical data not reported). [55]

We found one additional three-armed unblinded RCT (115 women with unilateral or bilateral hydrosalpinges), comparing surgery (laparoscopic proximal tubal occlusion [50 women] or salpingectomy [50 women]) with no treatment (15 women) before IVF in women with hydrosalpinges. [56] It found that proximal tubal occlusion before IVF significantly increased implantation rate, clinical pregnancy rate, and ongoing-pregnancy rate compared with no treatment before IVF (implantation: 20% with surgery *v* 6% with no treatment; OR 4.1, 95% CI 0.9 to 18.4; clinical pregnancy: 44% with surgery *v* 14% with no treatment; OR 4.8, 95% CI 0.9 to 23.9; ongoing pregnancy: 38% with surgery *v* 7% with no treatment; OR 7.9, 95% CI 0.9 to 65.8; absolute numbers not reported). It found that salpingectomy before IVF significantly increased implantation, clinical pregnancy, and ongoing pregnancy compared with no treatment before IVF (implantation rate: 25% with surgery *v* 6% with no treatment; OR 5.6, 95% CI 1.3 to 24.7; clinical pregnancy rate: 55% with surgery *v* 14% with no treatment; OR 7.4, 95% CI 1.5 to 36.9; ongoing pregnancy rate: 49% with surgery *v* 7% with no treatment; OR 12.5, 95% CI 1.5 to 103.1; absolute numbers not reported). [56] The RCT

stated that proximal tubal occlusion was carried out laparoscopically with bipolar diathermy applied on the isthmic segment at two separate sites and the hydrosalpinx was not drained. All the salpingectomies were done laparoscopically. [56] The variation between numbers of participants in the three groups (50, 50, 15 women) casts doubt on the claim that this study was randomised.

Different types of tubal surgery versus each other:
We found one systematic review (search date 2005, 7 RCTs). [53] The review did not pool the data. Many of the included RCTs were small, used outdated surgical techniques, and had problems relating to methods of randomisation, and therefore did not meet *Clinical Evidence* inclusion criteria. These data precede recent improvements in case selection and laparoscopic training. One RCT (63 women) identified by the review found no significant difference in pregnancy rates between CO_2 laser adhesiolysis and diathermy adhesiolysis (16/30 [53%] with laser *v* 17/33 [52%] with diathermy; OR 1.07, 95% CI 0.40 to 2.87). Another RCT (67 women) found no significant difference in pregnancy rates between CO_2 laser salpingostomy and diathermy salpingostomy (11/37 [30%] with laser *v* 7/30 [23%] with diathermy; OR for pregnancy 1.38, 95% CI 0.47 to 4.05). [53] A third RCT (240 women) compared the use of thermocoagulation versus electrocoagulation for adhesiolysis. It found no significant difference between the two groups at 6 months in pregnancy rates (32/120 [27%] with thermocoagulation *v* 37/120 [31%] with electrocoagulation; OR 0.87, 95% CI 0.51 to 1.46). [53]

We found one subsequent unblinded three-armed RCT (115 women) comparing laparoscopic proximal tubal occlusion, laparoscopic salpingectomy for hydrosalpinges, and no treatment before IVF treatment (see above for full description of this study). It found no significant difference in implantation rates, clinical pregnancy rates, or ongoing pregnancy rates between groups (92 women: implantation rate: 20% with proximal tubal occlusion *v* 25% with salpingectomy; OR 1.4, 95% CI 0.7 to 2.5; clinical pregnancy rate: 44% with proximal tubal occlusion *v* 55% with salpingectomy; OR 1.5, 95% CI 0.7 to 3.5; ongoing pregnancy rate: 38% with proximal tubal occlusion *v* 49% with salpingectomy; OR 1.6, 95% CI 0.7 to 3.6, absolute results not reported). [56]

Tubal surgery versus IVF:
We found two systematic reviews, which found no RCTs. [53] [54]

Harms:

Tubal surgery versus no treatment or medical treatment:
The review found no significant difference between tubal surgery and no treatment or medical treatment in the rate of ectopic pregnancy, miscarriage per pregnancy, or treatment-related complications (ectopic pregnancy: OR 0.42, 95% CI 0.08 to 2.14; miscarriage: OR 0.49, 95% CI 0.16 to 1.52; complications: OR 5.80, 95% CI 0.35 to 96.79). [55] Tubal surgery involves general anaesthesia and admission to hospital. There is a risk of ectopic pregnancy caused by pre-existing tubal damage; retrospective studies have reported rates of 7% to 9% with tubal surgery, compared with 1% to 3% with IVF. [57] [58] IVF carries the risk of multiple pregnancy and ovarian hyperstimulation syndrome (see harms of IVF under treatments for tubal infertility, p 25).

The additional RCT found no significant difference in miscarriage or ectopic pregnancy with proximal tubal occlusion versus no treatment (miscarriage rate: 4% with proximal tubal occlusion *v* 7% with no treatment; OR 0.6, 95% CI 0.05 to 7.2; ectopic pregnancy rate: OR 1.1, 95% CI 0.9 to 1.1). It also found no significant difference in miscarriage rate with salpingectomy versus no treatment (6% with salpingectomy *v* 7% without treatment; OR 0.9, 95% CI 0.08 to 9.3). [56]

Different types of tubal surgery versus each other:
The RCT in the updated systematic review showed infection rate to be significantly reduced when hydrotubation was carried with antibiotic compared with hydrotubation without antibiotic (1 RCT; 0/91 [0%] with hydrotubation with antibiotic *v* 23/100 [23%] with hydrotubation without antibiotic; OR 0.12, 95% CI 0.05 to 0.28). [53]

The additional RCT found no significant difference in miscarriage or ectopic pregnancy with proximal tubal occlusion versus salpingectomy (miscarriage: OR 1.5, 95% CI 0.2 to 9.2; ectopic pregnancy: OR 0.9, 95% CI 0.9 to 1.1). [56]

Tubal surgery versus IVF:
We found no RCTs.

Comment:

Different types of tubal surgery versus each other:
One additional systematic review (search date not reported, 7 observational studies, 279 women with proximal tubal blockage) compared microsurgery (275 women) versus macrosurgery (104 women). [48] It found that microsurgery significantly increased pregnancy rates compared with macrosurgery (RR 2.2, 95% CI 1.5 to 3.2).

Clinical guide:
Success rates with tubal surgery depend on the severity and site of disease. The best figures from surgery in women with distal tubal occlusion are live birth rates of 20% to 30%, with rates of 40% to 60% reported for the less common proximal occlusion. [59] [60] [61] [62] [63]

Tubal surgery versus IVF:
Fertility rates from case series of tubal surgery and from large databases of couples having IVF suggest that tubal surgery is as effective as IVF in women with filmy adhesions, mild distal tubal occlusion, or proximal obstruction. [59] [64] [65] [66] [67] [68] If successful, tubal surgery allows women to have more pregnancies without further medical intervention and without the risks associated with IVF. [69]

Adding postoperative treatments to tubal surgery:
We found one systematic review (search date 2008, 5 RCTs, 588 women) comparing early postoperative hydrotubation or second-look laparoscopy plus adhesiolysis after tubal surgery versus control (late postoperative hydrotubation, postoperative irrigation with antibiotics plus late postoperative hydrotubation, no postoperative hydrotubation, or no second look laparoscopy). [70] It found that all the RCTs were either poor quality or underpowered. One three-armed RCT (206 women), identified by the review, compared postoperative hydrotubation with corticosteroid versus hydrotubation without corticosteroid versus no hydrotubation after tubal surgery. It found no significant difference in pregnancy, live birth, ectopic pregnancy, or miscarriage rates between hydrotubation (with or without corticosteroids) and no hydrotubation after 24 months. It also found no significant difference in these outcomes between hydrotubation with corticosteroid and hydrotubation without corticosteroid. A second three-armed RCT, identified by the review, compared early postoperative hydrotubation versus late hydrotubation versus late hydrotubation with antibiotic (gentamicin). It found that hydrotubation with antibiotic significantly increased pregnancy rate and live birth rate compared with hydrotubation without antibiotic. However, it found no significant difference in ectopic pregnancy rates between hydrotubation with antibiotics and hydrotubation without antibiotics. It found no significant difference in pregnancy rate or live birth rate between early hydrotubation and late hydrotubation (no antibiotic). However, early hydrotubation was associated with significantly increased infective morbidity compared with late non-antibiotic hydrotubation. [70] The review pooled data from two RCTs comparing second-look laparoscopy with adhesiolysis versus no second-look laparoscopy. The review found no significant difference in pregnancy, live birth, ectopic pregnancy, or miscarriage rates between groups. [70]

OPTION IN VITRO FERTILISATION (IVF) IN TUBAL OBSTRUCTION FOR TUBAL INFERTILITY

Note
We found no clinically important results from RCTs about the effects of in vitro fertilisation (IVF) compared with no treatment or with tubal surgery in women with tubal infertility alone.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

In vitro fertilisation (IVF) versus no treatment:
We found no systematic review or RCTs.

Immediate versus delayed IVF:
We found one RCT (399 couples with any cause of infertility; the couples who received delayed IVF acted as untreated controls for at least 6 months). [71] The RCT did not present results separately for women with tubal obstruction (see comment).

IVF versus tubal surgery:
We found no RCTs. See comment of tubal surgery for tubal infertility, p 23 .

Harms:

IVF versus no treatment:
We found no RCTs.

Immediate versus delayed IVF:
The RCT found no difference between treatments in the overall rate of miscarriage or ectopic pregnancy; however, the study may have been too small to detect a clinically important difference (miscarriage: 6/33 [18%] with immediate IVF *v* 2/13 [15%] with delayed IVF; significance not reported; ectopic pregnancy: 5/33 [15%] with immediate IVF *v* 3/13 [23%] with delayed IVF; significance not reported). [71]

IVF versus tubal surgery:
We found no RCTs. See comment of tubal surgery for tubal infertility, p 23 .

Comment:

Immediate versus delayed in vitro fertilisation (IVF) in infertility of any cause:
The RCT (399 couples with any cause of infertility; the couples who received delayed IVF acted as untreated controls for at least 6 months), found that immediate IVF significantly increased pregnancy rate and number of live births compared with delayed IVF (pregnancy rate: 33/190 [17%] with immediate IVF *v* 13/163 [8%] with delayed IVF; RR 2.43, 95% CI 1.18 to 5.07; number of live births: 22/190 [12%] with immediate IVF *v* 8/163 [5%] with delayed IVF; RR 2.36, 95% CI 1.03 to 5.66). [71]

IVF versus ICSI:
We found one systematic review (search date 2002, 1 RCT), which compared IVF (224 cycles assessed) versus ICSI (211 cycles assessed) in women with various causes of infertility including tubal infertility. [72] The RCT found no significant difference in pregnancy rates between treatments. It found no significant difference between treatments in multiple pregnancy rate. [72] [73] It found that ovarian hyperstimulation syndrome occurred in seven (4%) IVF cycles and nine (5%) ICSI cycles (significance not reported). [73]

Clinical guide:
The success of IVF is influenced by a woman's age, duration of infertility, and previous pregnancy history. [8] Pregnancy rates are highest between the ages of 25 and 35 years and decline steeply after 35 years. Similar clinics, which describe the same methods, report different success rates for IVF. [8] In the UK Human Fertilisation and Embryology Authority database, the average live birth rate per IVF cycle in 2006–2007 was 24%, ICSI representing 48% of all IVF treatment in the UK in 2007. The remainder were conventional IVF, [74] if ICSI cycles were taken into account. [75] The equivalent average figure in the USA is 36%, [76] but again results vary among centres. [77] [78] In the UK, larger centres (200 or more cycles a year) report slightly higher live birth rates than smaller centres (20–29% variation among centres in the UK). [79] Such a difference has not been reported consistently in the USA.

Multiple births:
Of the 6309 live births after IVF in the UK in 2000–2001, 27% were multiple, including 109 (2%) triplets. [75] Of the 11,091 successful births giving rise to 13,672 babies after IVF in the UK in 2007, 23% were multiple births. In the UK, the number of embryos that can be replaced is restricted to two. [75] In the USA, where there are no such restrictions, 15 367 live births included 38% multiple births, 6% of which were triplets and above. [77] Of 54,656 infants born through assisted reproductive technology, 48% were multiple-birth deliveries.

Ovarian hyperstimulation syndrome:
One non-systematic review suggested that severe ovarian hyperstimulation syndrome (OHSS) occurs in 0.5% to 2% of all IVF cycles. [80] Another report for the UK Human Fertilisation and Embryology Authority in 2005, updated in 2008, found that severe OHSS occurs in approximately 1% of cycles. [81]

Obstetric outcome:
We found one systematic review (search date 1998, 42 high-quality observational studies) that compared obstetric outcome in mothers receiving IVF versus either a population-based control group or a selected control group matched for different variables. [82] It found that children born after IVF had a considerably higher risk of being born preterm and with a lower birth weight than children conceived naturally, although this was likely to be because of the high incidence of multiple births and maternal characteristics such as nulliparity, increased age, previous infertility, and obstetric history (absolute numbers not reported). There was no evidence of an increased overall incidence of congenital malformations in children born after conventional IVF or after embryo cryopreservation.

QUESTION What are the effects of treatments for infertility associated with endometriosis?

OPTION DRUG-INDUCED OVARIAN SUPPRESSION FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS

Pregnancy rate
Compared with placebo Ovulation-suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives, danazol, and gonadotrophin-releasing hormone [GnRH] analogue) seem no more effective at increasing pregnancy rates in women with endometriosis (moderate-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Drug-induced ovarian suppression versus placebo:
We found one systematic review (search date 2009, 11 RCTs, 557 women with visually diagnosed endometriosis who had been attempting conception for >12 months), which compared ovulation suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives, danazol, and gonadotrophin-releasing hormone [GnRH] analogues) versus placebo. It found no significant difference in pregnancy rates between ovulation suppression agents and placebo (80/287 [28%] with suppression agents *v* 73/270 [27%] with placebo; OR 1.02, 95% CI 0.69 to 1.50). [83]

Drug-induced ovarian suppression versus surgery:
See benefits of laparoscopic ablation of endometrial deposits, p 28 .

Harms:

Drug-induced ovarian suppression versus placebo:
The review did not report on the incidence of adverse effects in the included studies and did not pool the data on adverse effects. It reported that GnRH analogue causes hot flushes, vaginal dryness, headache, nasal congestion, and bone loss; danazol has a dose-related adverse effect of weight gain besides androgenic adverse effects. Weight gain, lack of libido, and depressed mood are the adverse effects of progestins. Oral contraceptives increase the risk of thromboembolism. [83]

Drug-induced ovarian suppression versus surgery:
See harms of laparoscopic ablation of endometrial deposits, p 28 .

Comment:

The results reported in the review suggest the use of ovulation suppression has no significant effect on endometriosis-related infertility. Expectant treatment is preferable over ovarian suppression because of its adverse effects. [83]

OPTION INTRAUTERINE INSEMINATION ALONE, OR COMBINED WITH GONADOTROPHINS OR CLOMIFENE FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS

Live birth rate
Compared with no treatment Intrauterine insemination (IUI) plus gonadotrophins (follicle-stimulating hormone [FSH]) is more effective than no treatment at increasing live birth rates in women with minimal or mild endometriosis (high-quality evidence).

Pregnancy rate
Compared with intrauterine insemination alone IUI plus gonadotrophins (FSH) is more effective than IUI alone at increasing pregnancy rates after the first treatment cycle in women with endometriosis (high-quality evidence).

Compared with no treatment/expectant management Intrauterine insemination plus clomifene may be more effective than expectant management at increasing pregnancy rates in women with surgically corrected endometriosis (low-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Intrauterine insemination (IUI) plus gonadotrophins versus no treatment or expectant management:
We found one RCT. [84] The RCT (103 couples with infertility associated with minimal or mild endometriosis) compared IUI plus gonadotrophins (follicle-stimulating hormone [FSH] 53 couples, 127 cycles) versus no treatment (50 couples, 184 cycles). [84] It found that IUI plus FSH significantly increased live birth rate per cycle compared with no treatment (14/127 [11%] with IUI plus FSH *v* 4/184 [2%] with no treatment; OR 5.6, 95% CI 1.8 to 17.4). [84]

IUI plus gonadotrophins versus IUI alone:
We found one RCT (119 couples with primary pelvic or cervical factor infertility for a mean of 3.7 years, 57 couples with infertility associated with endometriosis), which compared alternate cycles of gonadotrophins (human menopausal gonadotrophin [hMG]) plus IUI versus IUI alone. [85] It found that hMG plus IUI significantly increased the pregnancy rate after the first treatment cycle compared with IUI alone (11/58 [19%] with hMG plus IUI *v* 0/61 [0%] with IUI alone; P = 0.0002). Subgroup analysis of the 57 couples with endometriosis found that hMG plus IUI significantly increased the pregnancy rate per cycle compared with IUI alone (15/127 [12%] with hMG plus IUI *v* 2/96 [2%] with IUI alone; RR 5.1, 95% CI 1.1 to 22.5). [85]

IUI plus clomifene versus no treatment or expectant management:
We found one crossover RCT (51 couples, 24/51 [48%] women with unexplained infertility and 27/51 [52%] with endometriosis, duration of infertility 1–3.5 years) comparing IUI plus clomifene citrate versus expectant management (instruction to have intercourse during the periovulatory period). [86] The couples were initially randomised to either four treatment cycles or four control cycles,

followed by cross over to the other arm of the study if no pregnancy occurred. The RCT found higher pregnancy rates with IUI plus clomifene compared with expectant management after the initial four cycles (pre-crossover results) but did not assess the significance of the difference (proportion of women who became pregnant: 8/23 [35%] with treatment *v* 4/28 [14%] with no treatment, significance not reported). It found that treatment significantly increased the monthly fecundity rate (calculated from the total number of pregnancies after all cycles) compared with no treatment (monthly fecundity rate [number of pregnancies/cycles]: 10% [14 pregnancies after 148 cycles] with treatment *v* 3% [5 pregnancies after 150 control cycles] with no treatment; P = 0.03). [86]

Harms:

IUI plus gonadotrophins versus no treatment or expectant management:
No cases of severe ovarian hyperstimulation were reported in the RCT. [84] The RCT also reported two twin births and one triplet birth with IUI plus FSH.

IUI plus gonadotrophins versus IUI alone:
The RCT reported a miscarriage rate of 24% and a multiple birth rate of 18% with gonadotrophin (hMG) plus IUI (data for IUI treatment alone not reported). No cases of severe ovarian hyperstimulation requiring hospital admission were reported in the RCT. [85]

IUI plus clomifene versus no treatment or expectant management:
The RCT found that there were two ectopic pregnancies (14%) with IUI plus clomifene compared with none with expectant management, but it did not assess the significance of this difference. No cases of severe ovarian hyperstimulation were reported in the RCT. [86]

Comment: None.

OPTION LAPAROSCOPIC SURGERY FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS

Pregnancy rate
Compared with no surgery Laparoscopic ablation or resection of endometrial deposits seems more effective than diagnostic laparoscopy at increasing live birth rates or ongoing pregnancy rates (moderate-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Laparoscopic surgery versus no surgery:
We found one systematic review (search date 2000–2001, 2 RCTs, 437 women), which compared laparoscopic surgery (ablation or resection of endometrial deposits) versus diagnostic laparoscopy (no surgery). [87] It found that laparoscopic surgery significantly increased the proportion of women who had a live birth or pregnancy continuing beyond 20 weeks compared with diagnostic laparoscopy (60/223 [27%] with laparoscopic surgery *v* 39/214 [18%] with diagnostic laparoscopy; RR 1.48, 95% CI 1.03 to 2.11).

Laparoscopic treatment of endometrioma versus no treatment for endometrioma:
We found one systematic review (search date 2007), which found no RCTs comparing laparoscopic treatment of endometrioma versus no treatment. [88] The systematic review identified several observational studies relevant for this comparison, for further information on these see comment.

We found another systematic review (search date 2007), which identified one RCT in women with endometrioma (3 cm or more in diameter) comparing two different methods of laparoscopic surgery (excision or ablation). [89] The review did not report a direct comparison of laparoscopic surgery (excision or ablation) versus no treatment. However, it reported on the ovarian response to stimulation with gonadotrophins of the surgically treated (excision or ablation) ovary compared with untreated ovary in each woman (see comment). [89]

Harms:

Laparoscopic surgery versus no surgery:
The review found no significant difference between laparoscopic surgery and diagnostic laparoscopy in the proportion of women who miscarried or who had operative complications (miscarriage: 15/223 [7%] with laparoscopic surgery *v* 11/214 [5%] with diagnostic laparoscopy; RR 1.31, 95% CI 0.62 to 2.78; operative complications: 3/172 [2%] with laparoscopic surgery *v* 1/169 [1%] with diagnostic laparoscopy; RR 2.95, 95% CI 0.31 to 28.06). [87]

Laparoscopic treatment of endometrioma versus no treatment for endometrioma:
The first systematic review found no RCTs. For information on adverse effects from observational studies see comment. The second review gave no information on adverse effects. [89]

Comment:

Laparoscopic treatment of endometrioma versus no treatment for endometrioma:
The first systematic review identified five observational studies (3 retrospective case-control studies, 1 prospective and 1 retrospective cohort study), comparing laparoscopic treatment of endometrioma

versus no treatment for endometrioma, before in vitro fertilisation (IVF). The review carried out a meta-analysis. We have included a comment on these results here, because of the paucity of RCT data. The review found no significant difference in clinical pregnancy rates following IVF among women who underwent surgical treatment versus no treatment for endometrioma (4 studies: 65/227 [29%] with treatment for endometrioma *v* 35/141 [39%] with no treatment for endometrioma; OR 1.34, 95% CI 0.82 to 2.20). [88] It also found no significant difference in the number of oocytes retrieved following stimulation or in requirement for gonadotrophin ampoules among women who underwent surgical treatment versus no treatment for endometrioma (number of oocytes retrieved: 3 studies; 402 cycles: WMD –1.53, 95% CI –3.23 to +0.17; gonadotrophin ampoule requirement: 2 studies; 158 cycles: WMD +1.55, 95% CI –9.21 to +12.31). [88]

The second review reported no significant difference in ovarian response to gonadotrophin stimulation between the ovary treated with laparoscopic ablation and the untreated ovary in each woman (1 RCT: 80 ovaries: WMD –0.20, 95% CI –0.90 to +0.50). [89] It also found no significant difference in ovarian response to gonadotrophin stimulation when the ovary treated with laparoscopic excisional surgery was compared with the untreated ovary in each woman (1 RCT: 140 ovaries: WMD 0, 95% CI –0.47 to +0.47). [89] We found another systematic review (search date 2005, 6 observational studies). It concluded that surgery for endometrioma may result in a decrease in the number of oocytes retrieved but the overall fertility outcomes were not affected. [90]

Laparoscopic ablation versus excision of endometrioma:
We found one systematic review (search date 2007, 3 RCTs) comparing laparoscopic ablation versus excision of endometrioma. It presented results for spontaneous pregnancy rates separately for the subgroup of women who desired to conceive, and found that excisions surgery significantly increased 12-month spontaneous pregnancy rates compared with ablative surgery (2 RCTs, 88 women: 22/41 [54%] with excisions surgery *v* 8/47 [17%] with ablative surgery; OR 5.24, 95% CI 1.92 to 14.27). [89] It also presented results separately in women who underwent fertility treatment (controlled ovarian hyperstimulation) after these two surgical modalities from one RCT. It found no significant difference in pregnancy rates between groups (pregnancy rate in women who underwent fertility treatment: 15/41 [37%] with excisions surgery *v* 7/24 [29%] for ablative surgery; OR 1.40, 95% CI 0.47 to 4.15). [89]

Clinical guide:
The risks and morbidity of surgery under general anaesthesia and of postoperative adhesion formation need to be balanced against the adverse effects of treatments involving ovarian suppression or stimulation.

OPTION IN VITRO FERTILISATION IN ENDOMETRIOSIS

We found no direct information from RCTs about whether IVF is better than no active treatment in women with infertility associated with endometriosis.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

In vitro fertilisation (IVF) versus no treatment:
We found no systematic review or RCTs that compared IVF versus no treatment in women with endometriosis-related infertility.

Immediate versus delayed IVF:
We found no systematic review or RCTs that compared immediate IVF versus delayed IVF solely in women with endometriosis-related infertility. For data on immediate IVF versus delayed IVF in women with any cause of infertility see benefits of IVF under treatments for tubal infertility, p 25 .

Harms:

See harms of in vitro fertilisation under treatments for tubal infertility, p 25 .

Comment:

We found one systematic review [91] and two retrospective cohort studies [92] [93] that examined the effects of endometriosis compared with other causes of infertility, or the effects of severity of endometriosis, on IVF outcome. The cohort studies found no significant difference in pregnancy rates between groups. [92] [93] The systematic review (search date 1999, 22 non-randomised studies) found that women with endometriosis were less likely to become pregnant than women with infertility because of blocked or damaged tubes (pregnancy assessed by human chorionic gonadotrophin levels; adjusted OR 0.56, 95% CI 0.44 to 0.70). [91] There is a need for properly controlled prospective randomised studies that present fertility rates with IVF in different stages of endometriosis using a validated classification system. Comparisons with assisted reproductive techniques are also required.

Prolonged downregulation versus regular IVF:
We found one systematic review (3 RCTs, 165 women with endometriosis undergoing IVF or intracytoplasmic sperm injection [ICSI]), which concluded that pituitary downregulation with gonadotrophin-releasing hormone (GnRH) agonist for 3 to 6 months significantly increased the clinical pregnancy rate. [94] As for the live birth rate, there was one RCT (67 women) with significant increase in live birth in favour of prolonged downregulation. [94] There was no significant difference in the dose of follicle-stimulating hormone (FSH) required or duration of administration.

GnRH antagonist versus GnRH agonist protocol for IVF:
We found one RCT (246 women with mild to moderate endometriosis or surgically treated endometrioma or untreated endometrioma) comparing GnRH agonist or GnRH antagonist. There was no significant difference in the clinical pregnancy rates when either of the protocols were used. The women treated with GnRH antagonists had a significantly lower number of metaphase II oocytes and embryos. [95]

OPTION TUBAL FLUSHING/UTERINE BATHING WITH CONTRAST MEDIA FOR INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS New

Live birth rate
Tubal flushing with oil soluble contrast media compared with no treatment/expectant management Tubal flushing with oil-based media may be more effective than no treatment at increasing live birth rates at 6 months in women with minimal or mild endometriosis (low-quality evidence).

Pregnancy rate
Tubal flushing with oil soluble contrast media compared with no treatment/expectant management Tubal flushing with oil-based media may be more effective than no treatment at increasing pregnancy rate at 6 months in women with minimal or mild endometriosis (low-quality evidence).

Note
We found no direct information from RCTs about whether tubal flushing with water-based media is better than no active treatment.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Tubal flushing with oil soluble contrast media versus no treatment/expectant management:
We found one systematic review (search date 2007, 1 RCT, 158 women with unexplained infertility or endometriosis who had been attempting conception for >12 months, 62 women with visually diagnosed mild endometriosis). The RCT reported a subgroup analysis in women with endometriosis. It found that tubal flushing significantly increased pregnancy rates compared with no treatment in women with endometriosis (12/25 [48%] with tubal flushing *v* 4/37 [11%] with no treatment; OR 6.76, 95% CI 2.14 to 21.35). The RCT also found that tubal flushing (oil soluble contrast media) significantly increased live birth rate compared with no treatment in women with endometriosis (10/25 [40%] with tubal flushing *v* 4/37 [11%] with no treatment; OR 5.17, 95% CI 1.55 to17.23). [51] A 2-year follow-up of the RCT identified by the review has been published separately. [96] It found no significant difference in pregnancy rate in the longer term (6–24 months) between women with endometriosis who had tubal flushing with oil soluble contrast media and those with no initial treatment. This suggests that the benefit in pregnancy rate is observed in the first 6 months after the procedure. However, these results should be interpreted with caution because a total of 21 women in the original endometriosis subgroup underwent further fertility treatment, and 6 were lost to follow-up between 6 to 24 months.

Tubal flushing with water soluble contrast media versus no treatment/expectant management:
We found one systematic review (search date 2007), which found no RCTs comparing tubal flushing with water soluble media versus no intervention in women with endometriosis. [51]

Harms:

Tubal flushing with oil soluble contrast media versus no treatment/expectant management:
The review gave no information on adverse effects of treatments for this comparison. [51]

Tubal flushing with water soluble contrast media versus no treatment/expectant management:
We found no RCTs.

Comment:

The mode of action of tubal flushing has not been clearly elucidated. It is believed to act by flushing out debris, affecting immunological milieu by altering peritoneal macrophages, or modulating the endometrial environment. [51] Further evidence is needed comparing tubal flushing with other fertility treatments. [51]

Tubal flushing with oil soluble contrast media versus no treatment/expectant management (women with any cause of infertility):
We found one systematic review (search date 2007), which compared tubal flushing with oil soluble media versus no intervention in women with various causes of infertility. [51] It found that tubal flushing with oil soluble media significantly increased pregnancy rate and live birth compared with no intervention (pregnancy: 3 RCTs; 58/195 [30%] with oil soluble media *v* 21/187 [11%] with no intervention; OR 3.30, 95% CI 2.00 to 5.43; live birth: 1 RCT; 23/73 [32%] with oil soluble media *v* 11/85 [13%] with no intervention; OR 2.98, 95% CI 1.40 to 6.37). The systematic review found no significant difference between treatments in miscarriage per pregnancy or ectopic pregnancy (miscarriage per pregnancy: 1 RCT: 4/28 [14%] with oil soluble media *v* 2/14 [14%] with no intervention; OR 1.00, 95% CI 0.16 to 6.12; ectopic pregnancy: 1 RCT: 1/73 [1%] with oil soluble media *v* 0/85 [0%] with no intervention; OR 8.71, 95% CI 0.17 to 443.93). [51] However, the number of ectopic pregnancies was small and the corresponding confidence interval was very wide.

Tubal flushing with water soluble media versus no intervention (women with any cause of infertility):
We found one systematic review (search date 2007), which found no RCTs comparing tubal flushing with water soluble media versus no intervention. [51] We found one subsequent unblinded RCT (334 women, mean age 31.9 years, duration of infertility 2.1 years) comparing the spontaneous pregnancy rates in women undergoing tubal flushing at HyCoSy with water soluble contrast media versus women having no flushing of the tubes, as part of infertility investigative work-up. [52] The RCT excluded women with severe tubal pathology, those aged 40 years or older, or with suspected anovulation or severe male factor infertility. It found no significant difference between groups in clinical pregnancy rates (49/168 [29%] with flushing *v* 44/166 [27%] with no flushing, difference +2.7%, 95% CI –6.9% to +12.3%). It also found no significant difference in live birth rates (38/168 [23%] with flushing *v* 34/166 [21%] with no flushing; difference +2.1%, 95% CI –6.7% to +10.9%).The RCT found no significant difference between groups in miscarriage rates (9/168 [5%] with flushing *v* 8/166 [5%] with no flushing; difference +0.6, 95% CI –4.2 to +5.2). There was one ectopic pregnancy in each group. [52]

Oil soluble contrast media versus water soluble contrast media (women with infertility due to endometriosis or with any cause of infertility):
We found one systematic review (search date 2007, 5 RCTs, women with infertility of any cause who had been attempting conception for >12 months). The review carried out a subgroup analysis of pregnancy rate in women with infertility due to endometriosis. However, this subgroup of women (8 women) was too small to make any reliable conclusions. [51] The review found that tubal flushing with oil soluble contrast media (OSCM) significantly increased live birth rates compared with tubal flushing with water soluble contrast media (WSCM) in women with infertility of any cause; however, this was of borderline significance (2 RCTs, 931 women: 83/371 [22%] with OSCM *v* 88/560 [16%] with WSCM; OR 1.49, 95% CI 1.05 to 2.11). It found no significant difference between groups for pregnancy rates in women with infertility of any cause (5 RCTs; 1454 women; 179/625 [29%] with oil soluble media *v* 197/829 [24%] with water soluble media; OR 1.21, 95% CI 0.95 to 1.54).

The review found that extravasation was significantly more frequent with OSCM versus WSCM (3 RCTs, 768 women: 24/272 [9%] with OSCM *v* 9/496 [2%] with WSCM; OR 5.41, 95% CI 2.57 to 11.37). It found no significant difference between groups in rates of infection; however, this was lower with OSCM (2 RCTs: women 1/226 [0.4%] with OSCM *v* 15/436 [3.4%] with WSCM; OR 0.34, 95% CI 0.11 to 1.05). It also found no significant difference between groups for miscarriage rates or ectopic pregnancy (miscarriage: 1 RCT, 158 women: 19/74 [26%] with OCSM *v* 25/84 [30%] with WSCM; OR 0.82, 95% CI 0.41 to 1.64; ectopic pregnancy: 1 RCT, 533 women: 2/273 [1%] with OSCM *v* 4/260 [2%] with WSCM; OR 0.49, 95% CI 0.10 to 2.42). [51]

The review found that a significantly lower proportion of women had procedural pain, or post-procedure bleeding with oil soluble media compared with water soluble media (immediate pain [within 24 hours]: OR 0.53, 95% CI 0.34 to 0.84; prolonged pain [lasting >24 hours from the procedure]: OR 0.26, 95% CI 0.15 to 0.45; post-procedure bleeding: 2 RCTs; 662 women: 93/226 [41%] with oil soluble media *v* 345/436 [79%] with water soluble media; OR 0.22, 95% CI 0.15 to 0.31). However, it found that intravasation was significantly more common with oil soluble media (3 RCTs; 768 women: 24/272 [9%] with oil soluble media *v* 9/496 [2%] with water soluble media; OR 5.41, 95% CI 2.57 to 11.37), although the review reported no serious sequelae from this. It found no significant difference in the proportion of women with infection between groups (2 RCTs; 662 women: 1/226 [0.4%] with oil soluble media *v* 15/436 [3.4%] with water soluble media; OR 0.34, 95% CI 0.11 to 1.05). [51]

The odds of obtaining a satisfactory image were significantly decreased for oil soluble media versus water soluble media for both the uterine cavity and the tubal ampulla (uterine cavity: 3 RCTs; 773 women: 154/279 [55%] with oil soluble media *v* 437/494 [89%] with water soluble media; OR 0.18,

95% CI 0.12 to 0.26; tubal ampulla: 3 RCTs; 830 women: 40/323 [12%] with oil soluble media *v* 419/507 [83%] with water soluble media; OR 0.05, 95% CI 0.04 to 0.07). [51] The RCTs comparing oil soluble versus water soluble media were statistically heterogeneous. [51]

Oil soluble plus water soluble contrast media versus water soluble media (women with infertility due to endometriosis or with any cause of infertility):
We found one systematic review (search date 2007, 5 RCTs, women with infertility of any cause who had been attempting conception for >12 months). The review carried out a subgroup analysis of pregnancy rate in women with infertility due to endometriosis. However, this subgroup of women (9 women) was too small to make any reliable conclusions. [51] The review found no significant difference in live birth rates or pregnancy rates between tubal flushing with OSCM plus WSCM and WSCM (live birth rates: 1 RCT, 399 women who had been attempting conception for >12 months: 29/133 [22%] with OSCM plus WSCM *v* 54/260 [21%] with WSCM; OR 1.06, 95% CI 0.64 to 1.77; pregnancy rates: 5 RCTs, 662 women: 104/263 [40%] with OSCM plus WSCM *v* 131/399 [33%] with WSCM; OR 1.28, 95% CI 0.92 to 1.79). [51] The review found no significant difference between groups for miscarriage rates or ectopic pregnancy (miscarriage: 1 RCT, 130 women: 15/46 [32%] with OSCM plus WSCM *v* 25/84 [30%] with WSCM; OR 1.14, 95% CI 0.53 to 2.48; ectopic pregnancy: 2 RCTs, 422 women: 1/148 [1%] with OSCM plus WSCM *v* 4/274 [1%] with WSCM; OR 0.54, 95% CI 0.08 to 3.45). [51] No data were available on other adverse effects of treatments.

Clinical guide:
Although only one small RCT was found solely in women with endometriosis (a priori specified subgroup in larger trial), the result was highly statistically significant. This remains an intervention that is not offered on a widespread basis.

QUESTION What are the effects of treatments for unexplained infertility?

OPTION CLOMIFENE IN UNEXPLAINED FERTILITY New

Live birth rate
Compared with placebo or expectant management Clomifene (clomiphene) is no more effective than no treatment/placebo at increasing live birth rate in women with unexplained infertility (high-quality evidence).

Pregnancy rate
Compared with placebo or expectant management Clomifene seems no more effective than no treatment/placebo at increasing pregnancy rates in women with unexplained infertility (moderate-quality evidence).

Compared with stimulated intrauterine insemination (IUI) We don't know whether clomifene-stimulated IUI or clomifene plus timed intercourse are more effective at increasing clinical pregnancy rate in women with unexplained infertility (low-quality evidence).

Note
Clomifene is associated with increased risks of multiple pregnancy. Clomifene treatment, especially after several cycles, may be associated with a slightly higher risk of neural tube defects and severe hypospadias in the offspring.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Clomifene versus placebo or expectant management:
We found one systematic review (search date 2006, 2 RCTs, one of these RCTs reported as a conference abstract) comparing clomifene citrate with no treatment or placebo. [97] The RCT identified as an abstract by the review was subsequently reported in full. [98] We have also reported this here because it gives information on the outcome of live birth rate and adverse effects (see harms below).

The review found no significant difference in clinical pregnancy rate between clomifene citrate and no treatment or placebo for four to six treatment cycles (2 RCTs, 460 women: 40/231 [17.3%] with clomifene citrate *v* 40/229 [17.5%] with no treatment or placebo; OR 0.99, 95% CI 0.61 to 1.60; P = 0.96). [97] The RCT subsequently reported in full additionally reported on live birth rate. This RCT (580 women with unexplained infertility) was a three-armed trial comparing clomifene or unstimulated intrauterine insemination (IUI) versus expectant management. It found no significant difference in live birth rate between clomifene for six treatment cycles versus expectant management for 6 months (385 women: 26/194 [14%] with clomifene *v* 32/193 [17%] with expectant management; OR 0.79, 95% CI 0.45 to 1.38; P = 0.49). [98]

Clomifene versus unstimulated IUI:
We found one three-armed RCT (580 women with unexplained infertility) comparing clomifene, unstimulated IUI, or expectant management. The RCT compared both clomifene and unstimulated IUI versus expectant management. It was not designed to directly compare clomifene versus unstimulated IUI unless each active treatment was found to be superior to expectant management, which was not found (see clomifene versus expectant management above, and unstimulated IUI versus expectant management). It found similar rates of live birth and clinical pregnancy with clomifene and unstimulated IUI (live birth rate: 26/194 [14%] with clomifene *v* 43/191 [23%] with unstimulated IUI; clinical pregnancy rate: 29/192 [15%] with clomifene *v* 43/191 [23%] with unstimulated IUI). [98]

Clomifene versus stimulated IUI:
See benefits of IUI combined with gonadotrophins or clomifene in unexplained infertility, p 35 .

Clomifene versus in vitro fertilisation (IVF):
We found one systematic review (search date 2004), which found no RCTs assessing IVF in unexplained infertility. [99] We found no RCTs.

Harms:

Clomifene versus placebo or expectant management:
The RCT identified by the review [97] and subsequently reported in full found no significant difference in rate of miscarriage between clomifene and expectant management at 6 months' follow-up (385 women: 10/38 [26%] with clomifene *v* 14/46 [30%] with no treatment; OR 0.82, 95% CI 0.23 to 2.87; P = 0.86). [98] It also found no significant difference between clomifene and expectant management in the incidence of multiple pregnancies at 6 months' follow-up (2/192 [1%] with clomifene *v* 2/193 [1%] with expectant management; OR 1.01, 95% CI 0.08 to 13.39; P = 1.0). [98]

The systematic review found no data on the occurrence of ovarian hyperstimulation syndrome (OHSS) in the included RCTs. [97] It did not report on congenital anomalies. [97] For further information on congenital anomalies from observational studies see comment below.

Clomifene versus unstimulated IUI:
The RCT found similar rates of miscarriage between clomifene and unstimulated IUI at 6 months' follow-up; however, it did not present a statistical analysis of the difference (see above) (385 women: 10/38 [26%] with clomifene *v* 9/55 [16%] with unstimulated IUI). [98] It also found similar rates of multiple pregnancies with clomifene and unstimulated IUI at 6 months' follow-up (2/192 [1%] with clomifene *v* 1/191 [1%] with unstimulated IUI). [98]

Clomifene versus stimulated IUI:
See harms of IUI combined with gonadotrophins or clomifene in unexplained infertility, p 35 .

Clomifene versus IVF:
We found no RCTs.

Comment:

We found no systematic review or RCTs giving information on the risk of ovarian cancer associated with clomifene. Concerns have been raised over a possible association between fertility drugs and ovarian cancer. [100] A case-cohort study has suggested a link with clomifene when used for more than 12 months. [101] This has been recently challenged by several cohort studies. [102] [103] [104] [105]

Congenital anomalies We found one systematic review (search date not reported), reporting observational data (case reports, case-control studies, and uncontrolled studies).The review commented that clomifene treatment in mothers, especially after several cycles, might be associated with a slightly higher risk of neural tube defects and severe hypospadias in their children. [106]

OPTION INTRAUTERINE INSEMINATION (IUI) WITHOUT OVARIAN STIMULATION IN UNEXPLAINED FERTILITY New

Live birth rate
Compared with expectant management Unstimulated intrauterine insemination (IUI) seems no more effective than expectant management at increasing live birth rate at 6 months in women with unexplained infertility (high-quality evidence).

Compared with in vitro fertilisation (IVF) Unstimulated IUI and IVF seem equally effective at increasing live birth rate (moderate-quality evidence).

Compared with stimulated IUI Unstimulated IUI is less effective than IUI stimulated with clomifene or gonadotrophins at increasing live birth after up to six treatment cycles (high-quality evidence).

Pregnancy rate
Compared with expectant management Unstimulated IUI is no more effective than expectant management at increasing clinical pregnancy rate in women with unexplained infertility (high-quality evidence).

Compared with stimulated IUI Unstimulated IUI is less effective than IUI stimulated with clomifene or gonadotrophins at increasing clinical pregnancy rates (high-quality evidence).

Note
Unstimulated IUI seems not to increase the risk of miscarriage, multiple pregnancy, or ectopic pregnancy in women with unexplained infertility.

For GRADE evaluation of interventions for female infertility, **see table, p 44** .

Benefits:

Unstimulated intrauterine insemination (IUI) versus expectant management:
We found one systematic review (search date 2005) [107] and one subsequent RCT [98] examining the effectiveness of unstimulated IUI. The systematic review found no RCTs meeting its inclusion criteria. We also found one non-systematic review (see comments).

The subsequent RCT (580 women with unexplained infertility) compared clomifene (clomiphene) or unstimulated IUI versus expectant management. [98] It found no significant difference in live birth rate between unstimulated IUI after 6 months of treatment cycles versus expectant management for 6 months (43/191 [23%] with unstimulated IUI *v* 32/193 [17%] with expectant management; OR 1.46, 95% CI 0.88 to 2.43; P = 0.18). It also found no significant difference in clinical pregnancy rates between the two groups (43/191 [23%] with unstimulated IUI *v* 33/193 [17%] with expectant management; OR 1.41, 96% CI 0.73 to 2.74; P = 0.23). [98]

Unstimulated IUI versus clomifene:
See benefits of clomifene, p 32 .

Unstimulated IUI versus in vitro fertilisation (IVF):
We found one systematic review (search date 2005) which identified one three-armed RCT (258 couples randomised) comparing unstimulated IUI versus IVF versus stimulated IUI. [99] It found no significant difference in the live birth rate per woman/couple between IVF and IUI after six cycles (24/59 [41%] with IVF *v* 14/54 [26%] with unstimulated IUI; OR 1.96, 95% CI 0.88 to 4.36; P = 0.1). [99] The systematic review provided no data on clinical pregnancy from this RCT (see comment). [99] The review concluded that any effect of IVF relative to IUI with or without ovarian stimulation in terms of live birth rates for couples with unexplained subfertility remains unknown. The trial included in the review was limited by small sample size such that clinically significant differences cannot be ruled out.

Unstimulated IUI versus stimulated IUI:
See benefits of stimulated IUI, p 35 .

Harms:

Unstimulated IUI versus expectant management:
The subsequent RCT found no significant difference between unstimulated IUI and expectant management in the risk of miscarriage or multiple pregnancy after 6 months (miscarriage: 9/55 [16%] with unstimulated IUI *v* 14/46 [30%] with expectant management; OR 0.45, 95% CI 0.13 to 1.56; P = 0.1; multiple pregnancy: 1/193 [1%] with unstimulated IUI *v* 2/193 [1%] with expectant management; OR 0.05, 95% CI 0.02 to 11.92; P = 1.0). [98]

Unstimulated IUI versus clomifene:
See harms of clomifene, p 32 .

Unstimulated IUI versus IVF:
The systematic review gave no information on adverse effects. [99]

Unstimulated IUI versus stimulated IUI:
See harms of stimulated IUI, p 35 .

Comment:

Unstimulated IUI versus expectant management:
We excluded one review [108] that identified four RCTs as it was not a systematic review although it included a meta-analysis. One of the RCTs included in the meta-analysis was excluded by the earlier systematic review [107] because it did not present data per woman, and only reported biochemical pregnancies. Moreover, there was significant heterogeneity among the population within the included studies. [108]

OPTION INTRAUTERINE INSEMINATION COMBINED WITH GONADOTROPHINS OR CLOMIFENE IN UNEXPLAINED FERTILITY

New

Live birth rate

Compared with unstimulated intrauterine insemination (IUI) IUI cycles stimulated with clomifene or gonadotrophins are more effective at increasing live birth rate after up to six treatment cycles (high-quality evidence).

Compared with in vitro fertilisation (IVF) Stimulated IUI and IVF seem to be equally effective at increasing live birth rate (moderate-quality evidence).

Pregnancy rate

Compared with expectant management We don't know whether IUI cycles stimulated with clomifene are more effective than expectant management at increasing clinical pregnancy rate in women with unexplained infertility (low-quality evidence).

Compared with clomifene We don't know whether clomifene-stimulated IUI or clomifene plus timed intercourse is more effective at increasing clinical pregnancy rate in women with unexplained infertility (low-quality evidence).

Compared with unstimulated IUI IUI cycles stimulated with clomifene or gonadotrophins may be more effective at increasing clinical pregnancy rate (high-quality evidence). Note: Stimulated intrauterine insemination may increase ovarian hyperstimulation syndrome and multiple pregnancies.

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

Stimulated intrauterine insemination (IUI) versus expectant management:
We found one systematic review (search date 2005), which found one RCT (67 women with unexplained infertility and endometriosis randomised, 51 women analysed, duration of infertility 1–3.5 years and up to 8 treatment cycles each). [107] It found no significant difference between stimulated IUI and expectant management (timed intercourse in a natural cycle) after all cycles (pregnancy rate per couple after number of cycles: 8/23 [35%] after 73 cycles with stimulated IUI *v* 4/28 [14%] after 103 cycles with expectant management; OR 3.20, 95% CI 0.82 to 12.50; P = 0.09). The RCT identified by the review did not report on live birth rate for this comparison. [107]

Stimulated IUI versus clomifene:
We found one systematic review (search date 2005) comparing stimulated IUI (using clomifene, gonadotrophins, or clomifene plus gonadotrophins) versus timed intercourse using stimulated cycles (by the same regimen). [107] Subgroup analysis comparing clomifene-stimulated IUI versus clomifene plus timed intercourse found no significant difference in clinical pregnancy rates between groups (1 RCT, 40 couples with unexplained infertility: 1/17 [6%] with clomifene-stimulated IUI *v* 4/23 [17%] with clomifene plus timed intercourse only; OR 0.30, 95% CI 0.03 to 2.93; P = 0.3). [107]

Stimulated IUI versus unstimulated IUI:
We found one systematic review (search date 2005, 4 RCTs, 396 couples with unexplained infertility) comparing clomifene or gonadotrophins plus IUI (stimulated IUI) with unstimulated IUI for up to six cycles. [107] It found that stimulated IUI significantly increased live birth rate compared with unstimulated IUI after all cycles (50/202 [25%] with stimulated IUI *v* 27/194 [14%] with unstimulated IUI; OR 2.07, 95% CI 1.22 to 3.50; P = 0.006). [107] It found that stimulated IUI significantly increased clinical pregnancy rate compared with unstimulated IUI after all treatment cycles (51/202 [25%] with stimulated IUI *v* 27/194 [14%] with unstimulated IUI; OR 2.14, 95% CI 1.26 to 3.61; P = 0.004). [107]

Stimulated IUI versus IVF:
We found one systematic review (search date 2005), which identified one three-armed RCT (258 couples randomised) comparing stimulated IUI versus in vitro fertilisation (IVF) versus unstimulated IUI. [99] It found no significant difference between IVF and stimulated IUI in live birth rates (24/59 [41%] with IVF *v* 22/59 [37%] with stimulated IUI; OR 1.15, 95% CI 0.55 to 2.4). The systematic review provided no data on clinical pregnancy from this RCT and concluded that any effect of IVF relative to IUI with or without ovarian stimulation in terms of live birth rates for couples with unexplained subfertility remains unproven. [99] The study was limited by small sample size such that it was not possible to exclude clinically significant differences.

Harms:

Stimulated IUI versus expectant management:
The systematic review reported no multiple pregnancies and no cases of ovarian hyperstimulation syndrome (OHSS) in the identified RCT. The RCT did not report on miscarriage rates or ectopic pregnancies. [107] The authors of the review commented that there were insufficient data to investigate whether adverse effects (including multiple pregnancies, miscarriage, ectopic pregnancies, and OHSS) were associated with stimulated or unstimulated IUI. [107]

Stimulated IUI versus clomifene:
The review found no significant difference in multiple pregnancies between clomifene-stimulated IUI and clomifene plus timed intercourse (1 RCT: multiple pregnancies: 0/17 [0%] with IUI plus clomifene *v* 1/23 [4%] with timed intercourse plus clomifene; OR 0.43, 95% CI 0.02 to 11.18). [107] However, the authors of the review commented that there were insufficient data to investigate whether adverse effects (including multiple pregnancies, miscarriage, ectopic pregnancies, and OHSS) were associated with stimulated or unstimulated IUI. [107]

Stimulated IUI versus unstimulated IUI:
The review found no significant difference in multiple pregnancies, miscarriage, or ectopic pregnancy rate between clomifene-stimulated IUI and unstimulated IUI (multiple pregnancies: 2 RCTs: 1/30 [3%] with stimulated IUI *v* 0/35 [0%] with unstimulated IUI; OR 3.00, 95% CI 0.11 to 78.27; miscarriage: 1 RCT: 1/10 [10%] with stimulated IUI *v* 0/16 [0%] with unstimulated IUI; OR 5.21, 95% CI 0.19 to 141.08; ectopic pregnancy: 3 RCTs: 3/141 [2%] with stimulated IUI *v* 0/135 [0%] with unstimulated IUI; OR 6.48, 95% CI 0.33 to 127.09). [107] However, the authors of the review commented that there were insufficient data to investigate whether adverse effects (including multiple pregnancies, miscarriage, ectopic pregnancies, and OHSS) were associated with stimulated or unstimulated IUI. [107]

Stimulated IUI versus IVF:
The review found no significant increase in multiple pregnancies with IVF compared with stimulated IUI (12/59 [20%] with IVF *v* 17/59 [29%] with stimulated IUI; OR 0.63, 95% CI 0.27 to 1.47; P = 0.3). [99] It also found no significant difference in the incidence of OHSS per woman with IVF compared with stimulated IUI (3/59 [5%] with IVF *v* 2/59 [3%] with stimulated IUI; OR 1.53, 95% CI 0.25 to 9.49). [99]

Comment: None.

OPTION IN VITRO FERTILISATION AND EMBRYO TRANSFER (IVF-ET) IN UNEXPLAINED FERTILITY
N e w

Live birth rate
Compared with expectant management In vitro fertilisation (IVF) seems more effective at increasing live birth rate in women with unexplained infertility, however, evidence is insufficient to make any conclusions (moderate-quality evidence).

Compared with stimulated intrauterine insemination (IUI) We don't know whether IVF or stimulated IUI is more effective at increasing live birth rate, because evidence is insufficient to make any conclusions (moderate-quality evidence).

Compared with unstimulated IUI We don't know whether IVF or unstimulated IUI is more effective at increasing live birth rate, because evidence is insufficient to make any conclusions (moderate-quality evidence).

Pregnancy rate
Compared with placebo or expectant management IVF seems more effective than expectant management at increasing pregnancy rates in women with unexplained infertility (moderate-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 44 .

Benefits:

In vitro fertilisation (IVF) versus placebo or expectant management:
We found one systematic review (search date 2004, 2 RCTs). [99] The systematic review found that IVF significantly increased live birth rates compared with expectant management (1 RCT, 51 women: 11/24 [46%] with IVF *v* 1/27 [4%] with expectant management; OR 22.0, 95% CI 2.56 to 189.37). It found that IVF significantly increased clinical pregnancy rates compared with expectant management (2 RCTs, 86 women: 13/45 [29%] with IVF *v* 5/41 [12%] with expectant management; OR 3.24, 95% CI 1.07 to 9.80). [99] The review concluded that any effect of IVF relative to expectant management, clomifene citrate, and IUI with or without ovarian stimulation in terms of live birth rates for couples with unexplained subfertility remains unknown. The included RCTs were limited by their small sample size so that even large differences might be hidden. The review also commented on unequal follow-up between groups in the included RCTs — one RCT compared a single cycle of IVF treatment with 6 months of expectant management, the other RCT compared one cycle of IVF and 3 months of expectant management.

IVF versus unstimulated IUI:
See benefits of IUI, p 33 .

IVF versus stimulated IUI:
See benefits of IUI combined with gonadotrophins or clomifene, p 35 .

IVF versus clomifene:
See benefits of clomifene, p 32 .

Harms:

IVF versus expectant management:
The review gave no information on adverse effects. [99]

IVF is known to be associated with several potential complications, including ovarian hyperstimulation syndrome (OHS) and multiple pregnancy. For information from observational studies on the risk of breast cancer and perinatal adverse effects with IVF see comment below.

IVF versus unstimulated IUI:
See harms of IUI, p 33 .

IVF versus stimulated IUI:
See harms of IUI combined with gonadotrophins or clomifene, p 35 .

IVF versus clomifene:
See harms of clomifene, p 32 .

Comment:

Although a Cochrane systematic review for the effectiveness of IVF in unexplained infertility failed to provide data from RCTs as regard most IVF complications, IVF is known to be associated with several potential complications. Multiple pregnancy rate (including twins and triplets) associated with IVF is approximately 21%. [109] Ovarian hyperstimulation syndrome (OHSS), a potentially life-threatening adverse effect of ovulation induction, is another known complication of this treatment.

Breast cancer We found one systematic review, which presented a combined analysis of cohort studies (60,050 women treated with ovulation induction/IVF). It found no significant association between IVF treatments and increased risk of breast cancer (601 with observed *v* 568 with expected; RR 1.06; P = 0.337). Combined analysis of case-control studies (11,303 women in the breast cancer groups and 10,930 controls). Women in the breast cancer groups were slightly but not significantly less likely to have received IVF (2.2% with breast cancer *v* 2.5% with no breast cancer; RR 0.88; P = 0.231). [110]

Perinatal adverse effects (in singleton pregnancies) We found one systematic review (15 studies comprising 12,283 IVF and 1.9 million spontaneously conceived singletons). [111] Compared with spontaneous conceptions, IVF singleton pregnancies were associated with significantly higher odds of each of the perinatal outcomes examined: perinatal mortality (OR 2.2, 95% CI 1.6 to 3.0), preterm delivery (OR 2.0, 95% CI 1.7 to 2.2), low birth weight (OR 1.8, 95% CI 1.4 to 2.2), very low birth weight (OR 2.7, 95% CI 2.3 to 3.1), and small for gestational age (OR 1.6, 95% CI 1.3 to 2.0). Statistical heterogeneity was noted only for preterm delivery and low birth weight. Sensitivity analyses showed no significant changes in results. Early preterm delivery, spontaneous preterm delivery, placenta previa, gestational diabetes, preeclampsia, and neonatal intensive care admission were also significantly more prevalent in the IVF group. [111]

GLOSSARY

Delayed in vitro fertilisation In vitro fertilisation treatment after 6 months of being assessed in an infertility clinic after at least 12 months of infertility.

Gonadotrophin priming of oocytes This is the in vitro maturation of oocytes using gonadotrophins (hormones stimulate and control reproductive activity) from the germinal vesicle (early) stage of development to the metaphase II (mature) stage.

Hydrosalpinges is the abnormal distension of one or both fallopian tubes owing to fluid build up, usually because of inflammation.

Hydrotubation Flushing of the fallopian tubes through the cervix and uterine cavity to remove surgical debris and reduce the incidence of tubal reocclusion.

Immediate in vitro fertilisation In vitro fertilisation treatment within 6 months of being assessed in an infertility clinic after at least 12 months of infertility.

In vitro fertilisation (IVF) is a technique where female oocytes (eggs) are fertilised with sperm from a male partner outside the body in a fluid medium in the laboratory. Embryos are transferred later to the uterus using a special catheter.

Macrosurgery Surgery without dedicated optical magnification.

Microsurgery Surgery involving optical magnification to allow the use of much finer instruments and suture material in addition to a non-touch technique, with the aim of minimising tissue handling and damage.

Polycystic ovary syndrome (PCOS) results from an accumulation of incompletely developed follicles in the ovaries owing to chronic anovulation. PCOS is characterised by irregular or absent menstrual cycles, multiple small cysts on the ovaries (polycystic ovaries), mild hirsutism, and infertility. Many women also have increased insulin resistance.

Salpingography is a technique used to diagnose blockages in the fallopian tubes. It involves the radiographic imaging of the fallopian tubes after the injection of radio-opaque contrast medium (dye) through the cervix to the uterine cavity. If the fallopian tubes are open the dye flows into the tubes and then spills out to the abdominal cavity. This is documented in a series of x-ray images during the procedure. If tubes are blocked from the proximal end, a very narrow catheter is introduced under radiographic imaging (selective salpingography and tubal catheterisation) to remove the obstruction if possible.

Second look laparoscopy Laparoscopy performed some time after tubal surgery (either open or laparoscopic) with the aim of dividing adhesions relating to the initial procedure.

Tubal infertility is the inability to conceive owing to a blockage in one or both fallopian tubes and is a common cause of infertility. The tubal blockages are usually caused either by pelvic infection, such as pelvic inflammatory disease (PID) or endometriosis. Blockages may also be caused by scar tissue that forms after pelvic surgery.

Tubal surgery techniques are used to restore the patency of the fallopian tubes in women with tubal infertility as an alternative to in vitro fertilisation. Surgery may either be open microsurgery or laparoscopic microsurgery.

Anovulation is the failure to ovulate (expel a mature oocyte) owing to dysfunction of the ovary or suppression by drug treatment. Anovulation is a common cause of female infertility. Most often, women who do not ovulate also do not menstruate (amenorrhoea).

Assisted hatching procedure Assisted hatching is a process to breach the zona pellucida of an embryo, by either laser or chemical processes, potentially to improve its implantation potential.

Endometriosis is a progressive disease that occurs when the endometrial tissue lining the uterus grows outside the uterus and attaches to the ovaries, fallopian tubes, or other organs in the abdominal cavity. Symptoms include painful menstrual periods, abnormal menstrual bleeding, and pain during or after sexual intercourse.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Long agonist protocol is the most widely used protocol for an in vitro fertilisation (IVF) cycle, which involves starting the gonadotrophin-releasing hormone (GnRH) agonist usually on the 21st day of the menstrual cycle. Ovarian stimulation with follicle-stimulating hormone (FSH) then starts a couple of days after the onset of menstruation.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Ovarian hyperstimulation syndrome (OHSS) can occur in mild, moderate, and severe forms. Mild ovarian hyperstimulation syndrome is characterised by fluid accumulation, as shown by weight gain, abdominal distension, and discomfort. Moderate ovarian hyperstimulation syndrome is associated with nausea and vomiting, ovarian enlargement, abdominal distension, discomfort, and dyspnoea. Severe ovarian hyperstimulation syndrome is a life-threatening condition, in which there is contraction of the intravascular volume, tense ascites, pleural and pericardial effusions, severe haemoconcentration, and the development of hepatorenal failure. Deaths have occurred, caused usually by cerebrovascular thrombosis, renal failure, or cardiac tamponade.

Ovulation disorders are defined by the failure of an ovum to be expelled owing to a malfunction in the ovary. Ovulation disorders are a major cause of infertility and can often be corrected with medication. Ovulation disorders often result in infrequent menstruation (oligomenorrhoea).

Pituitary downregulation (long protocol) This is the process by which the release of gonadotrophins from the pituitary gland is stopped after repeated administration of gonadotrophin-releasing hormone (GnRH) analogues; this in turn controls reproductive function.

Pulsatile gonadotrophin-releasing hormone is a hormone produced and released by the hypothalamus at intervals (pulses). Pulsatile gonadotrophin-releasing hormone controls the production and release of gonadotrophins from the pituitary gland, which in turn controls reproductive function.

Tubal flushing involves injecting an oil or water soluble contrast medium into the fallopian tubes to flush out any blockages in the tubes. Flushing out any tubal "plugs" that may be causing proximal tubal occlusion using oil or water soluble media may have a fertility enhancing effect.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Tubal flushing for infertility associated with endometriosis New option added for which we found one systematic review that identified one RCT. [51] The RCT found that tubal flushing with oil soluble contrast media increased the pregnancy rate and live birth rate in minimal to mild endometriosis in the first 6 months. Categorised as Likely to be

beneficial as the results of the single RCT are supported by further data of the benefits of tubal flushing for infertility of any cause.

Clomifene in unexplained fertility New option, for which we found two systematic reviews [97] [99] and one three-armed RCT. [98] One review and subsequent RCT found no significant difference between clomifene and no treatment/placebo in pregnancy rate or live birth rate. [97] [98] Categorised as Likely to be ineffective or harmful.

Intrauterine insemination (IUI) alone in unexplained fertility New option added, for which we found one systematic review and one RCT comparing unstimulated IUI versus expectant management [107] [98] and one systematic review comparing unstimulated IUI versus in vitro fertilisation (IVF). [99] One RCT found no difference in live birth rate between unstimulated IUI and expectant management at 6 months. [98] One systematic review identified one three-armed RCT comparing unstimulated IUI versus IVF versus stimulated IUI. [99] It found no difference in the live birth rate per woman/couple between IVF and IUI. [99] Categorised as Likely to be ineffective or harmful.

Intrauterine insemination (IUI) combined with gonadotrophins or clomifene in unexplained fertility New option, for which we found two systematic reviews. [107] One review found no difference between stimulated IUI and expectant management (timed intercourse in a natural cycle) or timed intercourse using stimulated cycles. [107] It found that stimulated IUI increased live birth rate and clinical pregnancy rate compared with unstimulated IUI. [107] The second review found no difference between stimulated IUI and IVF in live birth rates. [99] Categorised as Trade-off between benefits and harms.

IVF-ET in unexplained fertility New option, for which we found one systematic review. [99] It found that IVF increased live birth rates and clinical pregnancy rates compared with expectant management. It found no difference in the live birth rate per woman/couple between IVF and unstimulated or stimulated IUI from one three-armed RCT. However, it concluded that any effect of IVF relative to expectant management, clomifene citrate and IUI with or without ovarian stimulation in terms of live-birth rates for couples with unexplained subfertility remains unknown. [99] Categorised as Unknown-effectiveness.

Clomifene for infertility caused by ovulation disorders One systematic review added comparing clomifene versus placebo, clomifene versus tamoxifen, or clomifene plus tamoxifen versus clomifene alone. [12] This review supersedes a previously reported review, and also includes two RCTs previously reported separately in this review. It found that clomifene citrate increased pregnancy rates and ovulation rates compared with placebo. It found no difference between clomifene and tamoxifen in pregnancy rate, ovulation rate, or live birth rate. [12] One RCT added comparing clomifene versus laparoscopic ovarian drilling (LOD). It found no difference between groups in ovulation rate per person after initial treatment. [14] One systematic review updated comparing clomifene versus metformin or versus metformin plus clomifene. [19] The review now includes additional RCTs compared with the previous version. It found that clomifene increased ovulation rate and pregnancy rate compared with metformin, but found no difference in live birth rate. It found that metformin plus clomifene improved ovulation rate and clinical pregnancy rate compared with clomifene alone, but found no difference between groups in live birth rate. Another systematic review added, [20] comparing metformin versus clomifene or metformin plus clomifene versus clomifene alone, which included many of the same studies as the first review, but performed a different analysis, and reached different conclusions. It found no difference between metformin versus clomifene or metformin plus clomifene versus clomifene in ovulation rate, clinical pregnancy rate, or live birth rate. One small subsequent RCT added, [21] which found no difference between clomifene plus metformin and clomifene plus placebo in ovulation rate after one to three cycles. Categorisation unchanged (Likely to be beneficial).

Drug-induced ovarian suppression for infertility associated with endometriosis One systematic review updated. [83] It now includes four additional RCTs, but the conclusion is unchanged. Categorisation unchanged (Likely to be ineffective or harmful).

Gonadotrophin priming of oocytes before in vitro maturation for infertility caused by ovulation disorders Previously included studies re-evaluated, one RCT [47] that did not meet *Clinical Evidence* inclusion criteria deleted. Categorisation unchanged (Unknown effectiveness).

Gonadotrophin-releasing hormone (GnRH) antagonists for infertility caused by ovulation disorders Two systematic reviews added comparing GnRH antagonists versus GnRH agonists in an in vitro fertilisation cycle. [31] [32] The review identified similar RCTs. They found no difference between groups in pregnancy rate or in live birth rate. Categorisation unchanged (Unknown effectiveness).

Gonadotrophins for infertility caused by ovulation disorders Two systematic reviews added, [25] [26] which found some of the same RCTs, and compared gonadotrophins plus metformin versus gonadotrophins alone. Another systematic review [27] added comparing urinary human chorionic gonadotrophin (hCG) versus no treatment in women being treated with clomifene citrate. One systematic review comparing laparoscopic ovarian drilling (LOD) versus gonadotrophins updated. [28] It now includes one RCT previously reported separately in this *Clinical Evidence* review; however, the conclusion is unchanged. One previously reported RCT comparing LOD versus a GnRH analogue plus a combined oral contraceptive re-evaluated and excluded from this section because it did not fulfil *Clinical Evidence* inclusion criteria. Previously reported text re-evaluated and data on women with any cause of infertility deleted from this section. Categorisation unchanged (Trade-off between benefits and harms).

In vitro fertilisation (IVF) for infertility caused by ovulation disorders One systematic review added comparing metformin plus IVF or intracytoplasmic sperm injection (ICSI) cycle versus no treatment/placebo plus IVF/ICSI in

women with polycystic ovary syndrome. [23] The review found no difference in live birth rate between adding metformin or adding placebo/no treatment to IVF/ICSI. Two systematic reviews added comparing GnRH antagonists versus GnRH agonists in an IVF cycle. [31] [32] The reviews identified similar RCTs. They found no difference between groups in pregnancy rate or live birth rate. Categorisation unchanged (Likely to be beneficial).

Intrauterine insemination (IUI) alone, or combined with gonadotrophins or clomifene for infertility associated with endometriosis One RCT added, [86] which compared IUI plus clomifene citrate versus expectant management. It found higher pregnancy rates with IUI plus clomifene compared with expectant management after four cycles. Categorisation unchanged (Likely to be beneficial).

Intrauterine insemination alone, or combined with gonadotrophins or clomifene for infertility caused by ovulation disorders One systematic review [42] added, which found no RCTs satisfying *Clinical Evidence* inclusion criteria. Comment added. Categorisation unchanged (Unknown effectiveness).

Laparoscopic surgery Two systematic reviews added, which found no RCTs comparing laparoscopic treatment of endometrioma versus no treatment. [88] [89] Comment added from these reviews on results from observational studies and one RCT comparing two different methods of laparoscopic surgery (excision or ablation). Categorisation unchanged (Likely to be beneficial).

Metformin for infertility caused by ovulation disorders One systematic review updated. [19] The review now includes additional RCTs compared with the previous version. It found that metformin increased pregnancy rate compared with placebo; however, it found no difference in live birth rate. It also found that clomifene increased ovulation rate and pregnancy rate compared with metformin, but found no difference in live birth rate. It found that metformin plus clomifene improved ovulation rate and clinical pregnancy rate compared with clomifene alone, but found no difference between groups in live birth rate. Another systematic review added, [20] comparing metformin versus clomifene or metformin plus clomifene versus clomifene alone, which included many of the same studies as the first review, but performed a different analysis, and reached different conclusions. It found no difference between metformin versus clomifene or metformin plus clomifene versus clomifene in ovulation rate, clinical pregnancy rate, or live birth rate. One small subsequent RCT added, [21] which found no difference between clomifene plus metformin and clomifene plus placebo in ovulation rate after one to three cycles. One systematic review added comparing metformin plus in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle versus no treatment/placebo plus IVF/ICSI in women with polycystic ovary syndrome (PCOS). [23] The review found no difference in live birth rate between adding metformin or adding placebo/no treatment to IVF/ICSI. Categorisation unchanged (Likely to be beneficial).

Tamoxifen for infertility caused by ovulation disorders One systematic review added. [12] This review includes two RCTs previously reported separately in this review. It found no difference between clomifene and tamoxifen in rates of pregnancy, ovulation, or live birth. Categorisation unchanged (Unknown effectiveness).

Tubal flushing with oil soluble media for tubal infertility One systematic review updated, [51] search date updated. Categorisation unchanged (Likely to be beneficial).

Tubal flushing with water soluble media for tubal infertility One systematic review updated, [51] search date updated. Categorisation unchanged (Unknown effectiveness).

Tubal surgery before in vitro fertilisation (IVF) for tubal infertility Two systematic reviews added. [53] [54] One previously reported systematic review updated, no new evidence found. [55] One additional RCT added comparing surgery (laparoscopic proximal tubal occlusion or salpingectomy) versus each other or versus no treatment. It found that proximal tubal occlusion and salpingectomy before IVF increased implantation rate, clinical pregnancy rate, and ongoing pregnancy rate compared with no treatment before IVF. It found no difference in implantation rates, clinical pregnancy rates, or ongoing pregnancy rates between surgeries. [56] One systematic review reported on RCTs comparing different types of surgery versus each other, but did not pool the data. [53] It found no difference in pregnancy rates between CO_2 laser adhesiolysis versus diathermy adhesiolysis, between CO_2 laser salpingostomy versus diathermy salpingostomy, or between thermocoagulation versus electrocoagulation for adhesiolysis, in RCTs. [53] Categorisation unchanged (Likely to be beneficial).

Laparoscopic ovarian drilling (LOD) for infertility caused by ovulation disorders One systematic review comparing LOD versus gonadotrophins updated. [28] It now includes one RCT previously reported separately in this *Clinical Evidence* review; however, the conclusion is unchanged, and it found no difference between LOD and gonadotrophins in live birth rate, pregnancy rate, or ovulation rate. One previously reported RCT comparing LOD versus a gonadotrophin-releasing hormone (GnRH) analogue plus a combined oral contraceptive re-evaluated and excluded from this section because it did not fulfil *Clinical Evidence* inclusion criteria. One systematic review added comparing LOD versus metformin or versus LOD plus metformin. [26] It found that metformin increased live birth rate compared with LOD. However, it found no difference between metformin versus ovarian drilling in clinical pregnancy rate. It found no difference between LOD versus LOD plus metformin in pregnancy rates or live birth rates. One RCT added comparing clomifene versus LOD. [14] It found no difference between groups in ovulation rate per person after initial treatment. Evidence re-evaluated. Categorisation changed from Unknown effectiveness to Likely to be beneficial.

Gonadotrophin-releasing hormone agonists plus gonadotrophins in ovulation disorders One systematic review [24] previously reported in another option in this *Clinical Evidence* review, also added to this option at update. It found no significant difference in ovulation rate or pregnancy rate between gonadotrophin alone or gonadotrophin plus GnRH agonist. It found increased incidence of overstimulation per cycle with gonadotrophin plus GnRH agonist. [24]

Previously reported studies in this *Clinical Evidence* review in women with infertility of various causes deleted from this option. Categorisation unchanged (Unknown effectiveness).

In vitro fertilisation in tubal obstruction Existing evidence re-evaluated, categorisation changed from Beneficial by consensus to Likely to be beneficial by consensus.

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Competing interests: SB is the author of several studies referenced in this review. NJ has been an author and co-author on several studies relating to endometriosis and infertility, which could be eligible for inclusion in the review. NJ has accepted travel grants within the past 5 years to attend conferences from the following companies: Seraon, Organan, and Device Technologies. RH is a member of the Fertility Advisory Board for Merck Serono and Schering-Plough, has received travel support from Merck Serono and Schering-Plough, and is a share holder of the company Fertility Specialists of Western Australia. HAT, SP, and AFG declare that they have no competing interests.
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Disclaimer

TABLE GRADE evaluation of interventions for female infertility

Important outcomes	Live birth rates, pregnancy rates, ovulation rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for infertility caused by ovulation disorders?									
3 (133) [12]	Pregnancy rate	Clomifene *v* placebo	4	–2	0	0	+2	High	Quality points deducted for sparse data and results post-crossover. Effect size points added for OR >5
3 (133) [12]	Ovulation rate	Clomifene *v* placebo	4	–2	0	0	+2	High	Quality points deducted for sparse data and results post-crossover. Effects size point added for OR >5
1 (95) [12]	Live birth rate	Clomifene *v* tamoxifen	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (256) [12] [13]	Pregnancy rate	Clomifene *v* tamoxifen	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (95) [12]	Ovulation rate	Clomifene *v* tamoxifen	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (72) [14]	Live birth rate	Clomifene *v* laparoscopic ovarian drilling	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for additional treatments
1 (72) [14]	Pregnancy rate	Clomifene *v* laparoscopic ovarian drilling	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for additional treatments
1 (72) [14]	Ovulation rate	Clomifene *v* laparoscopic ovarian drilling	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (50) [19]	Live birth rate	Metformin *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and low event rate leading to wide confidence intervals
6 (479) [19]	Pregnancy rate	Metformin *v* placebo	4	0	0	0	0	High	
13 (875) [19]	Ovulation rate	Metformin *v* placebo	4	0	0	0	0	High	
3 (600) [19] [20]	Live birth rate	Metformin *v* clomifene	4	–1	0	0	0	Moderate	Quality point deducted for significant statistical heterogeneity in analysis
3 (600) [19] [20]	Pregnancy rate	Metformin *v* clomifene	4	–1	–1	0	0	Low	Quality point deducted for significant statistical heterogeneity in analysis. Consistency point deducted for conflicting results
3 (594 women, 2470 cycles) [19] [20]	Ovulation rate	Metformin *v* clomifene	4	–1	–1	0	0	Low	Quality point deducted for significant statistical heterogeneity in analysis. Consistency point deducted for conflicting results
4 (752) [19] [20]	Live birth rate	Metformin plus clomifene *v* clomifene alone	4	0	0	0	0	High	
8 (976) [19] [20]	Pregnancy rate	Metformin plus clomifene *v* clomifene alone	4	–1	–1	0	0	Low	Quality point deducted for significant statistical heterogeneity. Consistency point deducted for different results between analyses
12 (2700) [19] [20] [21]	Ovulation rate	Metformin plus clomifene *v* clomifene alone	4	–1	–1	0	0	Low	Quality point deducted for significant statistical heterogeneity. Consistency point deducted for different results between analyses

Important outcomes	Live birth rates, pregnancy rates, ovulation rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
7 (627) [24]	Pregnancy rate	Urinary follicle-stimulating hormone *v* hMG	4	–2	0	0	0	Low	Quality points deducted for methodological weaknesses in included studies (blinding and method of randomisation not reported)
7 (627) [24]	Ovulation rate	Urinary follicle-stimulating hormone *v* hMG	4	–2	0	0	0	Low	Quality points deducted for methodological weaknesses in included studies (blinding and method of randomisation not reported)
3 (122) [26]	Live birth rate	Gonadotrophins plus metformin *v* gonadotrophins alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
at least 4 (at least 154) [25] [26]	Pregnancy rate	Gonadotrophins plus metformin *v* gonadotrophins alone	4	–2	0	0	0	Low	Quality points deducted for sparse data and inclusion of post-crossover results from one RCT
2 (305) [27]	Live birth rate	Urinary hCG plus clomifene citrate *v* clomifene citrate alone	4	–2	0	0	0	Low	Quality points deducted for methodological weakness in included RCTs (underpowered and no blinding)
2 (305) [27]	Pregnancy rate	Urinary hCG plus clomifene citrate *v* clomifene citrate alone	4	–2	0	0	0	Low	Quality points deducted for methodological weakness in one RCT (underpowered and no blinding)
2 (305) [27]	Ovulation rate	Urinary hCG plus clomifene citrate *v* clomifene citrate alone	4	–2	0	0	0	Low	Quality points deducted for methodological weakness in one RCT (underpowered and no blinding)
3 (211) [24]	Pregnancy rate	Gonadotrophin-releasing hormone agonists plus gonadotrophins *v* gonadotrophins alone	4	–2	0	0	0	Low	Quality points deducted for methodological weaknesses in included RCTs (not stating method of randomisation and lack of blinding)
3 (187) [24]	Ovulation rate	Gonadotrophin-releasing hormone agonists plus gonadotrophins *v* gonadotrophins alone	4	–3	0	0	0	Very low	Quality points deducted for sparse data and methodological weaknesses in included RCTs (not stating method of randomisation and lack of blinding)
2 (204) [32]	Live birth rate	Gonadotrophin-releasing hormone antagonists *v* gonadotrophin-releasing hormone agonists in an IVF cycle	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
4 (305) [31]	Pregnancy rate	Gonadotrophin-releasing hormone antagonists *v* gonadotrophin-releasing hormone agonists in an IVF cycle	4	–2	0	0	0	Low	Quality points deducted for inclusion of unpublished data and methodological flaws in 2 RCTs (not stating method of randomisation)
1 (28) [37]	Pregnancy rate	Pulsatile gonadotrophin-releasing hormone *v* clomifene	4	–2	0	0	0	Low	Quality points deducted for sparse data and methodological weaknesses
1 (28) [37]	Ovulation rate	Pulsatile gonadotrophin-releasing hormone *v* clomifene	4	–2	0	0	0	Low	Quality points deducted for sparse data and methodological weaknesses
2 (218) [28]	Live birth rate	Laparoscopic ovarian drilling *v* gonadotrophins	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of additional treatments in one RCT.
at least 3 (at least 254) [28]	Pregnancy rate	Laparoscopic ovarian drilling *v* gonadotrophins	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of additional treatments
1 (50) [28]	Ovulation rate	Laparoscopic ovarian drilling *v* gonadotrophins	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Live birth rates, pregnancy rates, ovulation rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (109) [26]	Live birth rate	Laparoscopic ovarian drilling *v* metformin	4	–1	0	0	0	Moderate	Quality points deducted for sparse data
2 (270) [26] [33]	Pregnancy rate	Laparoscopic ovarian drilling *v* metformin	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for inclusion of other treatments in one RCT
1 (161) [33]	Ovulation rate	Laparoscopic ovarian drilling *v* metformin	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting and sparse data. Directness point deducted for inclusion of other treatments in one RCT
1 (42) [26]	Live birth rate	Laparoscopic ovarian drilling *v* laparoscopic ovarian drilling plus metformin	4	–2	0	0	0	Low	Quality points deducted for sparse data and methodological weaknesses
1 (42) [26]	Pregnancy rate	Laparoscopic ovarian drilling *v* laparoscopic ovarian drilling plus metformin	4	–2	0	0	0	Low	Quality points deducted for sparse data and methodological weaknesses
3 (272) [23]	Live birth rate	Metformin plus IVF *v* IVF alone	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of ICSI in some studies
5 (426) [23]	Pregnancy rate	Metformin plus IVF *v* IVF alone	4	0	0	–2	0	Low	Directness points deducted for inclusion of ICSI in some studies and different result in subgroup analysis
3 (105) [43] [47] [45]	Pregnancy rates	Priming with gonadotrophins *v* no priming	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
What are the effects of treatments for tubal infertility?									
1 (31) [51]	Pregnancy rate	Tubal flushing with oil-based media *v* water-based	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis
3 (295) [55]	Live birth rate	Tubal surgery *v* no treatment/medical treatment	4	0	0	–2	+1	Moderate	Directness points deducted for narrow inclusion criteria and use of different comparators. Effect size point added for RR >2
3 (295) [55]	Pregnancy rate	Tubal surgery *v* no treatment/medical treatment	4	0	0	–2	0	Low	Directness points deducted for narrow inclusion criteria and use of different comparators
1 (63) [53]	Pregnancy rate	CO_2 laser adhesiolysis *v* diathermy adhesiolysis	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of treatments for infertility associated with endometriosis?									
11 (557) [83]	Pregnancy rate	Ovulation suppression *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for wide range of interventions
1 (103) [84]	Live birth rate	Intrauterine insemination plus gonadotrophins *v* no treatment	4	–1	0	–1	+2	High	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria. Effect size points added for OR >5
1 (57) [85]	Pregnancy rate	Intrauterine insemination plus gonadotrophins *v* intrauterine insemination alone	4	–1	0	0	+2	High	Quality point deducted for sparse data. Effect size points added for OR >5

Important outcomes	Live birth rates, pregnancy rates, ovulation rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (51) [86]	Pregnancy rate	Intrauterine insemination plus clomifene *v* no treatment/expectant management	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for no pre-crossover statistical assessment between groups
1 (62) [51]	Live birth rate	Tubal flushing with oil soluble contrast media *v* no treatment/expectant management	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis
1 (62) [51]	Pregnancy rate	Tubal flushing with oil soluble contrast media *v* no treatment/expectant management	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis
2 (437) [87]	Pregnancy rate	Laparoscopic surgery *v* no surgery	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
What are the effects of treatments for unexplained fertility?									
1 (387) [98]	Live birth rate	Clomifene *v* placebo/expectant management	4	0	0	0	0	High	
2 (460) [97]	Pregnancy rate	Clomifene *v* placebo/expectant management	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of one study published in abstract form
1 (384) [98]	Live birth rate	Unstimulated IUI *v* expectant management	4	0	0	0	0	High	
1 (384) [98]	Pregnancy rate	Unstimulated IUI *v* expectant management	4	0	0	0	0	High	
1 (113) [99]	Live birth rate	Unstimulated IUI *v* IVF	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (51) [107]	Pregnancy rate	Stimulated IUI *v* expectant management	4	–2	0	–1	+1	Low	Quality points deducted for sparse data and poor follow-up. Directness point deducted for inclusion of women with endometriosis. Effect size point added for effect size >2
1 (40) [107]	Pregnancy rate	Stimulated IUI *v* clomifene	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis
4 (396) [107]	Live birth rate	Stimulated IUI *v* unstimulated IUI	4	0	0	0	+1	High	Effect size point added for effect size >2
4 (396) [107]	Pregnancy rate	Stimulated IUI *v* unstimulated IUI	4	0	0	0	+1	High	Effect size point added for effect size >2
1 (118) [99]	Live birth rate	Stimulated IUI *v* IVF	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (51) [99]	Live birth rate	IVF *v* expectant management	4	–2	0	–1	+2	Moderate	Quality points deducted for sparse data and unequal follow-up between groups. Directness point deducted for uncertainty about significance of result. Effect size points added for effect size >5
2 (86) [99]	Pregnancy rate	IVF *v* expectant management	4	–2	0	0	+1	Moderate	Quality points deducted for sparse data and unequal follow-up between groups. Effect size point added for effect size >2

Type of evidence: 4 = RCT. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. Effect size: based on relative risk or odds ratio.
hCG, human chorionic gonadotrophin; hMG, human menopausal gonadotrophin; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilisation.