Clomiphene and anti-oestrogens for ovulation induction in PCOS (Review)

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[Intervention Review]

Clomiphene and anti-oestrogens for ovulation induction in PCOS

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ABSTRACT

Background

Subfertility due to anovulation is a common problem in women. First-line oral treatment is with anti-oestrogens, for example clomiphene citrate, but resistance (failure to ovulate) may be apparent with clomiphene. Alternative and adjunctive treatments have been developed such as tamoxifen, dexamethasone, and bromocriptine.

Objectives

To determine the relative effectiveness of anti-oestrogen agents alone or in combination with other medical therapies in women with subfertility associated with anovulation, possibly caused by polycystic ovarian syndrome (PCOS).

Search strategy

A search was conducted using the Cochrane Menstrual Disorders and Subfertility Group Trials Register (May 2009), CENTRAL (*The Cochrane Library* 2009, Issue 2), MEDLINE (1966 to May 2009), and EMBASE (1980 to May 2009) for identification of relevant randomised controlled trials (RCTs). The United Kingdom National Institute for Clinical Excellence (NICE) guidelines and the references of relevant reviews and RCTs were searched.

Selection criteria

RCTs comparing oral anti-oestrogen agents for ovulation induction (alone or in conjunction with medical therapies) in anovulatory subfertility were considered. Insulin sensitising agents, aromatase inhibitors, and hyperprolactinaemic infertility were excluded.

Data collection and analysis

Data extraction and quality assessment were done independently by two review authors. The primary outcome was live birth; secondary outcomes were pregnancy, ovulation, miscarriage, multiple pregnancy, overstimulation, ovarian hyperstimulation syndrome, and women reported adverse effects.

Main results

This is a substantive update of a previous review. Fifteen RCTs were included. One trial reported live birth. Miscarriage, multiple pregnancy rates and adverse events were poorly reported.

Clomiphene was effective in increasing pregnancy rate compared to placebo (OR 5.8, 95% CI 1.6 to 21.5) as was clomiphene plus dexamethasone treatment (OR 9.46, 95% CI 5.1 to 17.7) compared to clomiphene alone. No evidence of a difference in effect was found between clomiphene versus tamoxifen or clomiphene in conjunction with human chorionic gonadotrophin (hCG) versus clomiphene alone.

The remaining results had only one study in each comparison. A significant improvement in the pregnancy rate was reported for clomiphene plus combined oral contraceptives versus clomiphene alone. No evidence of a difference in effect on pregnancy rate was found with any of the other comparisons.

Authors' conclusions

This review shows evidence supporting the effectiveness of clomiphene citrate and clomiphene in combination with dexamethasone for pregnancy rate only. There is limited evidence on the effects of these drugs on outcomes such as miscarriage. Evidence in favour of these interventions is flawed due to the lack of evidence on live births.

PLAIN LANGUAGE SUMMARY

Clomiphene and anti-oestrogens for subfertility associated with anovulation

Subfertility due to the absence of ovulation is common for women. Medical treatment may help these women ovulate. Oral anti-oestrogens, for example clomiphene, cause increased stimulation of the ovaries and aid ovulation. The review of studies found evidence for the effectiveness of clomiphene. No evidence of a difference between clomiphene and tamoxifen, a similar anti-oestrogen drug, was found. Dexamethasone (a steroid) and combined oral contraceptives are both used to supplement clomiphene and show promise. Few studies reported beyond the establishment of early pregnancy so that, given the reported risks of miscarriage with clomiphene treatment, no definitive conclusions can be drawn about effective treatment. Evidence was inconsistent and further research is needed.

BACKGROUND

Description of the condition

Anovulation and oligo-ovulation are estimated to cause 21% of female infertility. Causes are split into three categories by the World Health Organization (WHO) (NICE 2004). These are:

- group one - hypothalamic pituitary failure or hypogonadotrophic hypogonadism, accounting for around 10% of ovulatory disorders;
- group two - hypothalamic pituitary dysfunction or eugonadotrophic, 85% of ovulatory disorders;
- group three - ovarian failure or hypergonadotropic hypogonadism, four to five % of ovulatory disorders.

Group two is the subject of this review. It consists predominantly of women with polycystic ovary syndrome (PCOS) but may also include women with hyperprolactinaemia and women with unexplained anovulation. PCOS is a common condition of uncertain aetiology that occurs in four % to seven % of women of reproductive age (Lobo 2000). The syndrome was first described in 1935 and was first known as Stein-Leventhal syndrome. The diagnostic criteria for PCOS have varied in the past. A recent consensus meeting between the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) (ESHRE/ASRM 2003) decided on the criteria, based upon majority opinion and not clinical trial data. Two of the following three factors are required for diagnosis of PCOS, with exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen secreting tumours, hyperprolactinaemia, and Cushing's syndrome:

- oligo-ovulation or anovulation;
- clinical or biochemical signs of hyperandrogenism, or both;
- polycystic ovaries as seen on ultrasound scanning (USS).

Common symptoms and signs of PCOS include hirsutism, acne, abnormal menstrual bleeding, and obesity. Investigations of women with PCOS may show raised luteinising hormone (LH) and testosterone levels. Features on USS are enlarged ovaries (volume > 10 ml) or ≥ 12 follicles 2 mm to 9 mm or greater in size diffusely distributed on one or both ovaries, or both (ESHRE/ASRM 2003). Women with PCOS may be at increased risk of pregnancy loss and complications, infertility, and endometrial carcinoma. Their cardiovascular risk is also raised due to an increased risk of type 2 diabetes mellitus, hypertension, and altered serum lipid profiles (ESHRE/ASRM 2003; Lobo 2000).

During normal menstruation, oestrogen levels are low while follicle stimulating hormone (FSH) and luteinising hormone (LH) levels begin to rise. This stimulates the development of an ovarian follicle which produces androgens (male sex hormones) some of which are bound to sex hormone binding globulin (SHBG) and some circulate freely in the bloodstream. Some androgens are converted to oestrogens. This causes a rise in the level of oestrogen which in turn causes a fall in FSH and LH levels. The oestrogen levels continue to rise eventually causing an LH surge which triggers ovulation. Following ovulation a corpus luteum is formed which produces progesterone as well as oestrogen.

In PCOS there is a state of chronic anovulation, characterised by small ovarian cysts, elevated ovarian production of androgens, and sometimes hypersecretion of LH. PCOS is the most common cause of anovulatory infertility. With the new criteria (ESHRE/ASRM 2003) being wider than previously accepted definitions its diagnosis is even more frequent.

Hyperprolactinaemia (which is included in the WHO group two category) is not included in this review.

Description of the intervention

A number of treatment options, used alone or in conjunction with other medical therapies, are available for the treatment of subfertility associated with anovulation.

Clomiphene citrate and tamoxifen

Medical ovulation induction with clomiphene citrate is at present the first-line treatment for anovulatory women. Clomiphene is an anti-oestrogen and competes for receptor binding sites with endogenous oestrogens. Recently published United Kingdom National Institute for Clinical Excellence (NICE) guidelines state that first-line treatment for WHO group two anovulation should be clomiphene (or tamoxifen) for up to 12 months (NICE 2004). The recommended daily dose of clomiphene is 50 to 100 mg with a maximum of 250 mg. However, clomiphene resistance (failure to ovulate after taking clomiphene) is common, occurring in approximately 15% to 40% of women with PCOS (Kousta 1997; Pritts 2002; Wolf 2000). Definitions vary but the NICE definition is: "Anovulatory women who do not ovulate while receiving the 150 mg dose of clomiphene citrate" (NICE 2004). Resistance is associated with an increased body mass index (BMI) and weight loss programmes improve the success rates of clomiphene therapy (Kousta 1997). Alternative and adjunctive treatments have been sought due to the high incidence of clomiphene resistance.

Dexamethasone as an adjunct

Addition of oral dexamethasone, a steroid hormone, to clomiphene therapy has been advocated to improve the chances of ovulation and subsequent pregnancy.

Bromocriptine as an adjunct

Bromocriptine, a dopamine agonist used to treat hyperprolactinaemia, has been studied as an adjunctive treatment to clomiphene-induced ovulation in anovulatory women with PCOS.

Aromatase inhibitors

The use of aromatase inhibitors (AIs) to treat anovulatory infertility is a new indication. Proponents of AIs believe that they are superior to, and safer than, clomiphene. The latest form of these drugs ('third generation' anastrozole, letrozole, and exemestane) are currently being used for the treatment of breast cancer (Mitwally 2004). Aromatase inhibitors are not included in this review as they are the subject of a separate protocol (El Daly 2006).

CYP17a inhibitors

Ketoconazole is a CYP17a Inhibitor. It inhibits a different part of the cytochrome P450 complex to AIs. Ketoconazole inhibits aromatase activity in the gonads (Hassan 2001; Parsanezhad 2003) and, therefore, may have similar effects to AIs with added anti-androgenic effects.

Metformin and other insulin sensitising agents alone or as an adjunct

A feature of PCOS is hyperinsulinaemia due to insulin resistance. This is thought to increase androgen production by the ovaries. Metformin and other insulin sensitising agents (for example troglitazone, rosiglitazone, pioglitazone, and D-chiro-inositol) are thought to help correct this and therefore increase ovulation and pregnancy rates in women with PCOS (Lord 2004). Use of insulin sensitising agents such as metformin were not included in this review as they are the subject of a separate review (Lord 2004).

Gonadotrophins

Human menopausal gonadotrophins (hMG) are a long-standing treatment for clomiphene resistant women. There are a variety of injectable drugs available (hMG, urinary FSH, and recombinant FSH). These all have problems with cost, risk of multiple pregnancy, and ovarian hyperstimulation syndrome (OHSS) (Bayram 2004a).

Pulsatile gonadotrophin releasing hormone (GnRH) is also sometimes used. This involves pulsatile GnRH infusion by the intravenous or subcutaneous route using a portable pump. Cost and effect is probably similar to that of hMG treatment (Bayram 2004b) but there may be a reduced risk of multiple pregnancy and OHSS (Tan 1996).

How the intervention might work

Clomiphene citrate and tamoxifen

By blocking receptors in the hypothalamus and pituitary, clomiphene interferes with the feedback mechanism of endogenous oestrogen on the pituitary and hypothalamus. An increase in FSH and LH secretion by the pituitary results. This stimulates the production of ovarian follicles and ovulation. Estimates for numbers of women conceiving with clomiphene therapy vary from 30% to 50% (Kousta 1997) to 15% (NICE 2004). Approximately 7% of pregnancies resulting from clomiphene-induced ovulation are twin pregnancies and 0.5% are triplet pregnancies (Wolf 2000). Miscarriage rates of 13% to 25% have been reported with clomiphene-induced conceptions (Kousta 1997). This proportion may be higher than in women with normal fertility and unassisted conception but this is uncertain (Oates-Whitehead 2003). A more advanced age may be responsible and beyond that it is not possible to separate the adverse effects of treatment from the underlying process leading to subfertility. OHSS has been reported rarely following clomiphene use. Tamoxifen has been used to induce ovulation (Messinis 1982) but is used much less frequently than clomiphene. Its mode of action is similar to that of clomiphene.

Dexamethasone as an adjunct

The proposed mechanism of action of dexamethasone in PCOS is suppression of the adrenal production of androgens, which should augment clomiphene's action. Secondly, it has been suggested that dexamethasone may facilitate the development of ovarian follicles by causing an increase in FSH levels. A third mechanism of action may be to reduce the high pulsatile levels of LH seen in PCOS and which contributes to anovulation (Brann 1991).

Bromocriptine as an adjunct

Dopamine can reduce elevated LH levels in PCOS (Leblanc 1976) and has also been reported to lead to a return in cyclical ovarian activity in normoprolactinaemic women with PCOS (Siebel 1984).

Why it is important to do this review

The available literature was reviewed in an attempt to establish the effectiveness and complications of anti-oestrogen agents, alone or in combination with adjunctive treatments, in ovulation induction for women with anovulatory infertility.

This review is intended to supercede the review on clomiphene citrate for ovulation induction (Hughes 1996) and covers WHO group two women.

OBJECTIVES

To determine the relative effectiveness of anti-oestrogen agents, with or without other medical therapies, in women with WHO group two anovulation (excluding hyperprolactinaemia).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) that compared oral agents for ovulation induction (alone or in conjunction with medical adjuncts) in anovulatory subfertility were considered for inclusion in the review.

Quasi-randomised trials were excluded. Cross-over trials were not included unless phase one data were available.

Types of participants

Women of reproductive age with WHO group two anovulation. Anovulation is defined as a lack of evidence of serum progesterone in the luteal range for the reference laboratory or a failure of basal body temperature to rise by > 0.4 °C for 10 days or more. Age was as determined by trial authors.

Exclusion criteria

Women with hyperprolactinaemia or Cushing's syndrome, or both, were excluded and trials which reported that women with these two conditions had been included were excluded from the review. Trials containing women with WHO group one anovulation were excluded.

Types of interventions

Anti-oestrogen versus no treatment or placebo

For example:

- clomiphene;
- tamoxifen;
- other.

Anti-oestrogen versus anti-oestrogen

For example:

- clomiphene versus tamoxifen;
- clomiphene versus other;
- tamoxifen versus other;
- other.

Anti-oestrogen plus other medical therapy versus anti-oestrogen alone

For example:

- dopamine agonist - bromocriptine;
- dopamine agonist - cabergoline;

- corticosteroid - dexamethasone;
- other.

Anti-oestrogen plus other medical therapy versus anti-oestrogen plus other medical therapy

Trials utilising intrauterine insemination were excluded as they are not part of the objective of this review. Trials utilising natural intercourse or timed intercourse were included.
Insulin sensitising agents such as metformin and aromatase inhibitors were not included in this review as they are the subject of separate reviews (Lord 2004; El Daly 2006).

Types of outcome measures

Primary outcomes

- Live birth rate (per woman)
- Miscarriage rate (per woman), where miscarriage was defined as the involuntary loss of a pregnancy before 20 weeks gestation

Secondary outcomes

- Pregnancy rate (per woman), where pregnancy was defined as evidence of intrauterine gestation on ultrasound; this includes pregnancies in the pre-treatment phase
- Ovulation rate (per woman), where ovulation was defined as evidence of serum progesterone in the luteal range for the reference laboratory or a basal body temperature rise by > 0.4 ºC for ten days or more as measured by a basal body temperature chart
- Incidence of multiple pregnancy (per woman), where multiple pregnancy was defined as greater than one intrauterine pregnancy
- Incidence of overstimulation (per woman), defined according the definition adopted by the reporting authors
- Incidence of women reported adverse effects (per woman), defined according the definition of the reporting authors

Definitions of the diagnosis of PCOS and the other studied outcomes in this review (ovulation, overstimulation, OHSS) were also recorded.

Search methods for identification of studies

This is a substantive update of the previous review and the following sources were searched for relevant studies.

Electronic searches

(1) Cochrane Menstrual Disorders and Subfertility Group Trials Register (searched 9th May 2009)
2) Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 2, 2009) for keyword: Anovulation (Appendix 4)
(3) MEDLINE, EMBASE, and PsycINFO databases for trials in all languages (Appendix 1, Appendix 2, Appendix 3)

Searching other resources

(1) NICE fertility assessment and treatment guidelines
(2) References of relevant systematic reviews and RCTs

Data collection and analysis

Selection of studies

In the update of this review, the trials to be included were independently selected by two review authors (JB, CF) in accordance with the aforementioned criteria. Trials were excluded from the systematic review if they made comparisons other than those specified above.

Data extraction and management

The following information was extracted from the included trials and presented in the table 'Characteristics of included studies'.

Trial characteristics

(a) Randomisation
(b) Allocation concealment
(c) Trial design: multicentre or single centre; single phase or cross-over design
(d) Number of women randomised, excluded, and analysed
(e) Duration, timing, and location of the trial
(f) Source of funding

Baseline characteristics of the studied groups

(a) Definition and duration of pre-existing infertility
(b) Age of the women
(c) Investigative work-up
(d) Other causes of infertility
(e) Previously administered treatment(s)

Intervention

(a) Type of intervention and control
(b) Dose regime

Outcomes

(a) Outcomes reported
(b) How are outcomes defined?
(c) How are outcomes measured?
(d) Timing of outcome measurement
All data in the updated review were extracted independently by two of the authors (JB, CF) using forms designed according to Cochrane guidelines. Additional information was sought on trial methodology and actual trial data from the authors of six trial reports (Boonstanfar 2001; Branigan 2003; Hassan 2001; Parsanezhad 2002a; Parsanezhad 2002b; Vegetti 1999); no reply was received. We were unable to contact the authors of five trial reports (Cudmore 1966; Daly 1984; Garcia 1985; Johnson 1966; Suginami 1993).
Where pregnancies occurred in the pre-treatment phase they were included as a success in the analysis.

Assessment of risk of bias in included studies

Trials were screened and analysed for the following quality criteria; this information is presented in both a quality table and the text of the review and helps to provide a context for discussing the reliability of results.

- Method and timing of randomisation: randomised (for example, by computer, random number table, or drawing lots), quasi-randomised (for example, by hospital number or date of birth), not clear (for example, stated but not further described). Trials rated as quasi-randomised were excluded.
- Concealment of allocation: adequate (for example, by third party or sealed opaque envelopes), inadequate (for example, open list of allocation codes), not clear (for example, not stated or 'envelopes' stated without further description).
- The use of blinding.
- Whether an intention-to-treat analysis was performed.

Measures of treatment effect

For dichotomous data (all the outcome measures in this review), results for each trial were expressed as an odds ratio (OR) with 95% confidence interval (CI).

Unit of analysis issues

Data were extracted as per woman randomised. Per cycle data were not pooled.
Only the first arm of cross-over trials was included in a pooled analysis.

Dealing with missing data

Where data were missing an attempt was made to contact the original study report authors.

Assessment of heterogeneity

Heterogeneity (variations) between the results of different trials was examined by inspecting the scatter in the data points on the graph and the overlap in their CIs and, more formally, by checking the results of the Chi^2 and I^2 statistics. I^2 describes the percentage of total variation across the trials which is due to heterogeneity rather than chance (Higgins 2002). Negative values are put to zero so that the value lies between 0% and 100%, where 0% represents no heterogeneity.
Where possible (that is where trials are sufficiently homogenous in participants and design) the results for each comparison have been pooled statistically. Where heterogeneity is above 50% data will not be pooled but explanatory analyses will be used through subgroup and sensitivity analysis to try and explain the source.

Assessment of reporting biases

All outcome measures stated in the methods section will be compared with those reported in the results section to ensure comparability. If there are sufficient trials a funnel plot will be produced.

Data synthesis

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration. Data was pooled where there was more than one study with available data. A fixed-effect model was used.

Subgroup analysis and investigation of heterogeneity

If a clinically important difference in drug regime (outside of normal clinical practice) occurred between trials an attempt would have been made to form dose subgroups for analysis. No such trials were found.
Trials performed on women with clomiphene-resistant PCOS only would also have been the subject of a subgroup analysis if more than two trials had been found for any of the comparisons.

Sensitivity analysis

Sensitivity analysis was conducted on the primary outcome measure of live birth.

Timeline

It is the intention of the review authors that a new search for RCTs will be performed every two years and the review updated accordingly.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

Please see Characteristics of included studies and Characteristics of excluded studies tables.

Included studies

Design

Fifteen trials were included in this review. Eleven were parallel-design RCTs (Boonstanfar 2001; Branigan 2003; Branigan 2005; Daly 1984; Elkind-Hirsch 2005; Elnashar 2006b; Hassan 2001; Parsanezhad 2002a; Parsanezhad 2002b; Vegetti 1999; Yilmaz 2006) and four were cross-over trials where phase-one data were available (Cudmore 1966; Garcia 1985; Johnson 1966; Suginami 1993).

Setting

A variety of different settings were used to recruit women into the studies.

- Not stated (Boonstanfar 2001; Cudmore 1966; Daly 1984; Johnson 1966; Hassan 2001; Suginami 1993).
- Infertility clinic (Branigan 2003; Branigan 2005; Vegetti 1999; Yilmaz 2006).
- Outpatient department (Elnashar 2006b).
- Department of obstetrics and gynaecology (Garcia 1985).
- Division of reproductive endocrinology (Parsanezhad 2002a).
- Women's health institute (Elkind-Hirsch 2005).

Country

The following is a list of countries in which the included studies were conducted.

- Turkey (Yilmaz 2006).
- USA and Canada (Boonstanfar 2001; Branigan 2003; Branigan 2005; Cudmore 1966; Daly 1984; Elkind-Hirsch 2005; Garcia 1985; Johnson 1966).
- Japan (Suginami 1993).
- Italy (Vegetti 1999).
- Iran (Parsanezhad 2002a).
- Eygpt (Elnashar 2006b; Hassan 2001).

Participants

Ages of the women ranged from 18 to 39 years. Age was not stated by Daly 1984.

Cycles of treatment

The number ranged from one to six plus in the included trials but was not stated in some trials.

- Not stated (Boonstanfar 2001; Daly 1984; Vegetti 1999).
- One (Branigan 2005; Elkind-Hirsch 2005; Elnashar 2006b; Johnson 1966; Suginami 1993; Yilmaz 2006).
- Up to three (Cudmore 1966).
- One to five (Garcia 1985).
- Six or more, or to pregnancy (Branigan 2003; Parsanezhad 2002a).
- Three to six (Hassan 2001).

Inclusion criteria

The main inclusion criteria listed in the trials are listed. Anovulatory PCOS was the principle inclusion criterion.

- Anovulatory (Boonstanfar 2001; Branigan 2003; Cudmore 1966; Daly 1984; Garcia 1985; Johnson 1966; Suginami 1993; Vegetti 1999).
- PCOS (Branigan 2005; Elnashar 2006b; Hassan 2001).
- Insulin resistance (Hassan 2001).
- Secondary amenorrhoea (> two years) or oligomenorrhoeic (Cudmore 1966; Daly 1984; Elkind-Hirsch 2005; Yilmaz 2006).
- No previous exposure to clomiphene or ovulation induction (Daly 1984; Yilmaz 2006).
- No fertility treatment in previous three months (Cudmore 1966).
- No other causes of infertility (Boonstanfar 2001; Branigan 2003; Cudmore 1966; Yilmaz 2006).
- Clomiphene-resistant PCOS (Parsanezhad 2002a).
- Normoprolactinaemia (Suginami 1993; Yilmaz 2006).
- Tubal patency (Branigan 2003).
- Specified ages (Branigan 2003; Branigan 2005; Elkind-Hirsch 2005; Elnashar 2006b; Yilmaz 2006).
- No medication for previous two months (Elnashar 2006b).
- Duration of primary infertility > two years (Elnashar 2006b; Yilmaz 2006).
- Normal semen analysis (Branigan 2005; Yilmaz 2006).
- Normal results on hysterosalpingogram (Branigan 2005; Yilmaz 2006).
- Normal endocrine function (Branigan 2005; Elnashar 2006b; Yilmaz 2006).
- BMI between 18 and 38 (Elkind-Hirsch 2005).

Interventions

Anti-oestrogen versus no treatment or placebo

Clomiphene versus placebo

Three trials compared clomiphene versus placebo (Cudmore 1966; Garcia 1985; Johnson 1966); all were of crossover design (phase-one data only). Doses varied from a 50 mg fixed dose to a variable dose of up to 250 mg (dependent on ovulatory response). Phase one of the trials lasted from one to five cycles. The number of participants was 133 in total, 63 randomised to the control group and 70 to the treatment group.

Anti-oestrogen versus anti-oestrogen

Clomiphene versus tamoxifen

Two trials compared clomiphene versus tamoxifen (Boonstanfar 2001; Vegetti 1999). Doses of clomiphene varied from 50 mg to 200 mg as both trials varied dose dependent on ovulatory response. Doses of tamoxifen varied from 20 mg to 60 mg, again as both trials varied the dose. Duration of treatment was not stated in either of the trials. The total number of cycles of treatment was between 91 and 129 for women on clomiphene and between 113 and 133 for tamoxifen. The Boonstanfar 2001 trial appears to have continued after publication in 2001. An abstract of a larger trial was published in 2002 which appears to include the women from Boonstanfar 2001. This abstract has been excluded from analysis while awaiting author clarification. One hundred and eighty-one women in total participated, 97 were randomised to clomiphene treatment and 84 to tamoxifen.

Clomiphene plus tamoxifen versus clomiphene

Suginami 1993 compared clomiphene plus tamoxifen versus clomiphene alone. The trial was of cross-over design with phase-one data available. The dose of clomiphene was 100 mg when used alone and 50 mg when used in combination with 20 mg tamoxifen. Up to three cycles of treatment were given in the first phase. Of the 20 participants, ten were randomised to clomiphene plus tamoxifen treatment and ten to clomiphene alone.

Anti-oestrogen plus other medical therapy versus anti-oestrogen alone

Clomiphene plus bromocriptine versus clomiphene

Parsanezhad 2002b compared clomiphene plus bromocriptine versus clomiphene. The control group were given 200 mg clomiphene and placebo continuously. The treatment group were given 200 mg clomiphene plus 7.5 mg bromocriptine continuously. Both groups were administered hCG (10,000 U) to trigger ovulation and were treated for up to six cycles. The dose of bromocriptine or placebo was gradually introduced before commencing clomiphene. All of the 100 participants had clomiphene-resistant PCOS, 53 were randomised to the control group and 47 to the treatment group.

Clomiphene plus dexamethasone versus clomiphene

Three trials compared clomiphene plus dexamethasone versus clomiphene (Daly 1984; Elnashar 2006b; Parsanezhad 2002a). The control groups were given 50 to 150 mg clomiphene on days five to nine (Daly 1984); 200 mg clomiphene on days five to nine and placebo from day five to day 14 (Parsanezhad 2002a); or 100 mg clomiphene on days three to seven and placebo from days three to 12 (Elnashar 2006b). Treatment groups were given 50 to 150 mg clomiphene plus 0.5 mg dexamethasone on days five to nine (Daly 1984); 200 mg clomiphene on days five to nine plus 2 mg dexamethasone on days five to 14 (Parsanezhad 2002a); or 100 mg clomiphene on days three to seven plus 2mg dexamethasone on days three to 12 (Elnashar 2006b). Human CG was administered to both groups to trigger ovulation in Parsanezhad 2002a and Elnashar 2006b . Both groups were treated for up to six cycles in Parsanezhad 2002a and for only one cycle in Elnashar 2006b. There were 355 participants in total, 181 were randomised to the control group and 174 to the treatment group.

Clomiphene plus ketoconazole versus clomiphene

Hassan 2001 compared clomiphene plus ketoconazole versus clomiphene. The control group were given up to 150 mg clomiphene for three to six cycles. The treatment group were given 400 mg/day ketoconazole for 85 days and then 100 to 150 mg clomiphene for three to six cycles. In both groups "patients who persistently failed to respond to clomiphene 150 mg per day (clomiphene resistant) were shifted to hMG". The 97 participants were all insulin resistant and had PCOS, 48 were randomised to the control group and 49 to the treatment group.

Clomiphene plus combined oral contraceptive versus clomiphene

Branigan 2003 compared clomiphene plus combined oral contraceptive (COC) versus clomiphene. The control group had no treatment for 38 to 56 days (two cycles), in particular no progestin to induce menstruation, while the treatment group were given COC (using Desogen: 0.03 mg ethinyl estradiol and 0.15 mg desogestrel) continuously for 42 to 50 days. In the following cycle each group received 100 mg clomiphene on days five to nine, with ovulation triggered by 10,000 U of hCG. Those women who ovulated but did not become pregnant in this cycle (from either group) repeated the clomiphene dose for up to six cycles. It was not clear what treatment or follow up was given for those who did not ovulate. The 51 participants were all clomiphene resistant; 25 were randomised to the control group and 26 to the treatment group.

Clomiphene plus *hCG* versus clomiphene alone

Two studies made this comparison (Branigan 2005; Yilmaz 2006). In the study by Branigan 2005 the experimental group received

clomiphene 100 mg daily from days five to nine with daily doses of 200 IU hCG intramuscularly; the control group received 150 mg clomiphene daily from days five to nine. Yilmaz 2006 administered 50 mg clomiphene from days five to nine with 10,000 IU hCG administered when the follicle reached > 18 mm in diameter; the control group received clomiphene only.

Clomiphene plus hormone supplementation versus clomiphene alone

One study was identified which made this comparison (Elkind-Hirsch 2005). The control and experimental groups both received clomiphene 100 mg daily from days three to seven. The experimental group received oral estradiol (E2) 1.5 mg twice daily commencing on day eight and discontinued when a LH surge was detected. Seventy-one women were randomised.

No RCTs were found for the following comparisons.

- Tamoxifen versus placebo.
- Any anti-oestrogen plus cabergoline versus anti-oestrogen.
- Any anti-oestrogen plus medical adjunct versus anti-oestrogen plus medical adjunct.

Outcomes

Live birth was reported in one trial (Boonstanfar 2001). All of the trials reported pregnancy and ovulation rate was reported in all but one trial (Hassan 2001). Six trials reported incidence of multiple pregnancy (Boonstanfar 2001; Branigan 2003; Daly 1984; Elnashar 2006b; Hassan 2001; Yilmaz 2006), eight (Cudmore 1966; Boonstanfar 2001; Branigan 2003; Elkind-Hirsch 2005; Elnashar 2006b; Hassan 2001; Vegetti 1999; Yilmaz 2006) reported adverse events including miscarriage or spontaneous abortion rate and two (Boonstanfar 2001; Suginami 1993) reported incidence of OHSS. None of the trials reported incidence of overstimulation.

Ovulation rate was often reported in an unclear form. Statements such as "In women who received bromocriptine, 18.3% ovulated as evidenced by progesterone levels" (Parsanezhad 2002b) were made. It is unclear whether these figures are per women, per cycle or some other rate. It has been assumed, where reasonable (i.e. when calculated as an actual figure, using total participants, a whole number resulted, this was considered in combination with analysis of the wording of the trial) that these figures are per women over the whole treatment period. Furthermore trials that reported ovulation rate per woman appear to have counted the first time only, however this is not totally clear.

Excluded studies

See Characteristics of excluded studies table.

Thirty-two trials initially identified were excluded from the review. The reasons were primarily due to their inclusion criteria, interventions and conference papers that were superceded by full papers.

Risk of bias in included studies

Please *see* Characteristics of included studies table and Figure 1 , Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

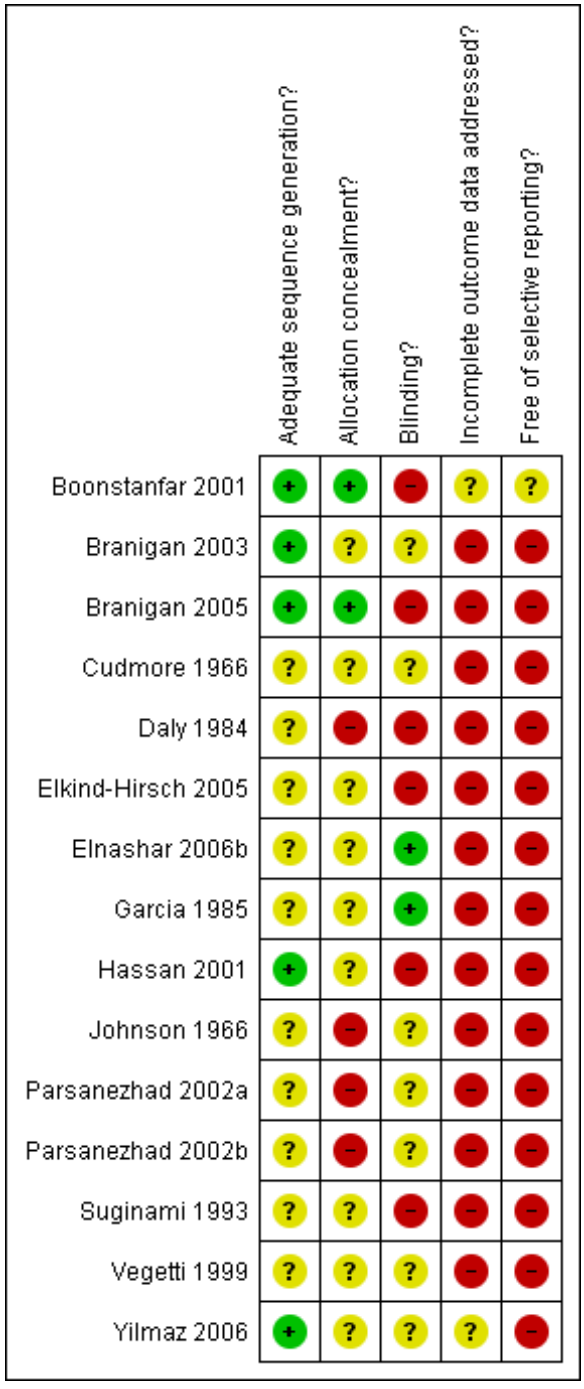
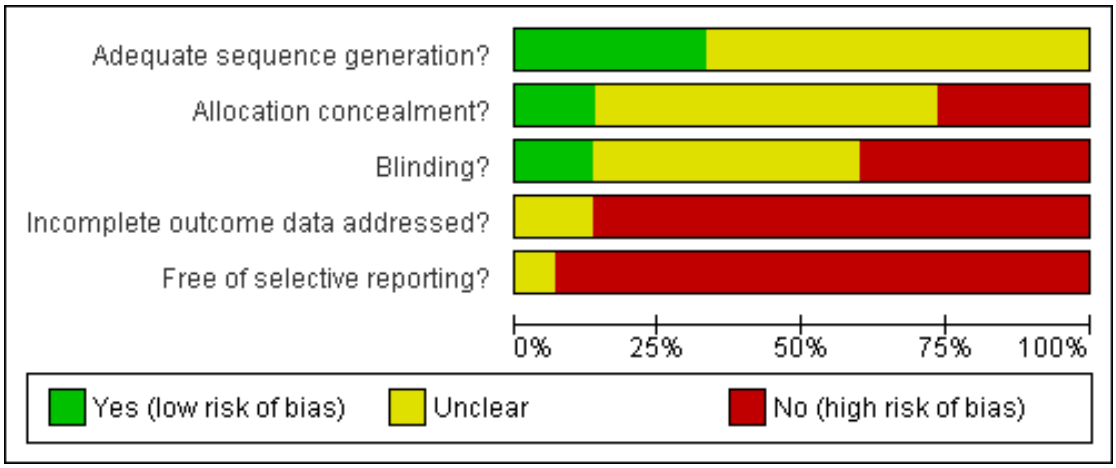


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Eleven studies were parallel-design RCTs (Boonstanfar 2001; Branigan 2003; Branigan 2005; Daly 1984; Elkind-Hirsch 2005; Elnashar 2006b; Hassan 2001; Parsanezhad 2002a; Parsanezhad 2002b; Vegetti 1999; Yilmaz 2006) and four were cross-over trials where phase-one data were available (Cudmore 1966; Garcia 1985; Johnson 1966; Suginami 1993). Five trials were graded A (adequate) for allocation concealment (Boonstanfar 2001; Branigan 2003; Branigan 2005; Elnashar 2006b; Yilmaz 2006), the remaining studies were unclear.

Blinding

Seven trials were described as double blind (Cudmore 1966; Elnashar 2006b; Garcia 1985; Johnson 1966; Parsanezhad 2002a; Parsanezhad 2002b; Yilmaz 2006) but it was not specified who was blinded to allocation. The remaining trials were open-labelled or missing details as to blinding.

Incomplete outcome data

For the purpose of this review a withdrawal was defined as a participant who stopped taking the assigned trial drug but was followed up by the trial. A loss to follow up was defined as a woman who stopped participating in the trial and was not followed up. The number of drop outs is both these figures together. However, these terms are often used interchangeably by trial authors, without being defined.

Only Garcia 1985 performed an intention-to-treat (ITT) analysis; the phase-one data contained results for all but three participants (who were lost to follow up). Two studies reported no drop outs and all women randomised were analysed (Elnashar 2006b; Suginami 1993). A rate of < 10% of participants dropping out would be considered an acceptable attrition rate; six studies reported rates from 4.3% to 10% (Boonstanfar 2001; Branigan 2003; Branigan 2005; Elkind-Hirsch 2005; Johnson 1966; Yilmaz 2006).

A rate of > 10% of participants dropping out may be a cause for concern. Daly 1984 (17%), Garcia 1985 (43%, though 94% of participants were analysed in phase-one data) and Hassan 2001(18%) all had high drop-out rates. The reasons are detailed in the 'Risk of bias' tables. Four trials (Cudmore 1966; Parsanezhad 2002a; Parsanezhad 2002b; Vegetti 1999) did not state whether any drop outs occurred. Parsanezhad 2002b presented outcome rates as percentages, an attempt to calculate actual participant numbers from the group sizes given at randomisation indicated that participants may have been lost to follow up.

Selective reporting

All of the studies reported on the main outcome of pregnancy and only one study did not report on ovulation rate (Hassan 2001). There were differences in the number of cycles of treatment (one

to six plus) and therefore the duration of the follow up. This has been detailed in the previous section of the review.

There were differences in the definitions used in some of the outcomes. This may have influenced reporting on these: PCOS, pregnancy, ovulation rate and clomiphene resistance (see table 'Characteristics of included studies' for details).

Other potential sources of bias

Source of funding

Pharmaceutical funding was declared by three trials (Cudmore 1966; Elkind-Hirsch 2005; Johnson 1966). Garcia 1985 received a research grant from the National Institute of Child Health and Human Development Institute. No other trial stated any source of funding.

None of the trials performed compliance monitoring to assess adherence to the treatment regimen.

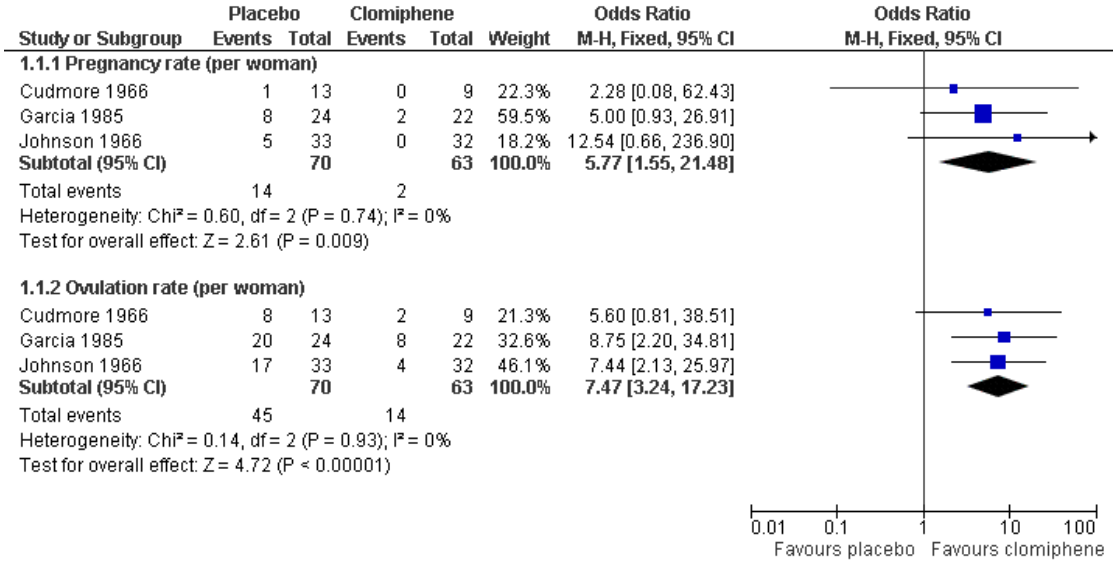
Effects of interventions

Anti-oestrogen versus no treatment or placebo

- Clomiphene (50 to 250 mg) versus placebo

Three trials compared clomiphene and placebo (Cudmore 1966; Garcia 1985; Johnson 1966). Only pregnancy and ovulation rates were reported for this comparison. I^2 was 0% for both outcomes. Analysis showed a large and consistent benefit of clomiphene compared to placebo (3 trials, 133 participants; fixed OR 5.77, 95% CI 1.55 to 21.48; P < 0.009) (see Figure 3). Analysis for ovulation rate (per woman) also showed a benefit of clomiphene compared with placebo (3 trials, 133 participants; fixed OR 7.47, 95% CI 3.24 to 17.23; P < 0.00001) (see Figure 3).

Figure 3. Forest plot of comparison: 1 Anti-oestrogen versus no treatment/placebo, outcome: 1.1 Clomiphene versus placebo.



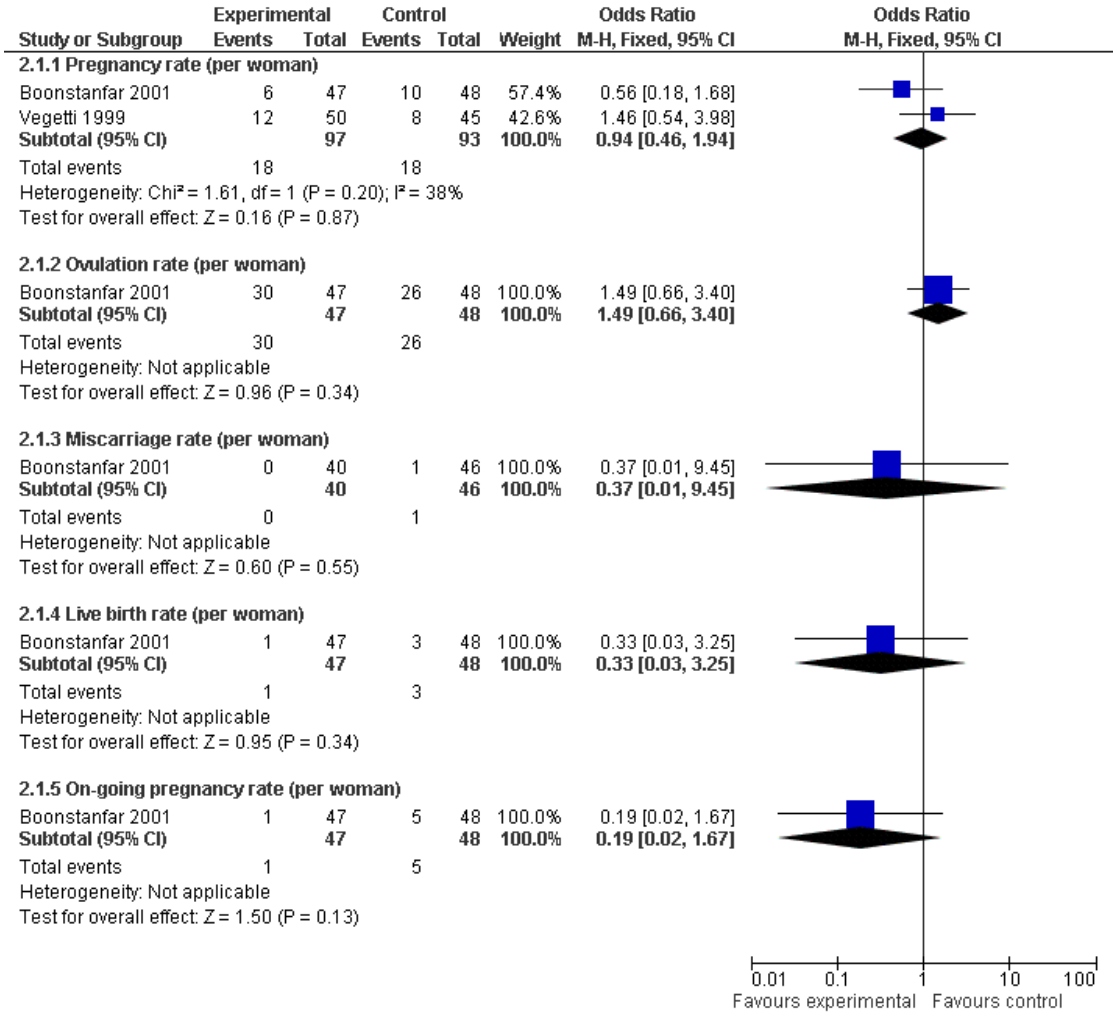
Anti-oestrogen versus anti-oestrogen

- Clomiphene (50 to 200 mg) versus tamoxifen (20 to 60 mg)

Two trials compared clomiphene and tamoxifen (Boonstanfar 2001; Vegetti 1999). Live birth rate (OR 0.33, 95% CI 0.03 to 3.25; P = NS) and ongoing pregnancy rate (OR 0.19, 95% CI 0.02 to 1.67; P = NS) were both reported by Boonstanfar 2001. There were no significant differences in pregnancy (Figure 4) (OR 0.94, 95% CI 0.46 to1.94; P = NS) or ovulation rate (OR 1.49, 95% CI 0.66 to 3.40; P = NS) between the two groups. There were no instances of OHSS or multiple pregnancies (Boonstanfar 2001) and there were no differences in the incidence of miscarriage in the one trial reporting this outcome (Boonstanfar 2001) (OR

0.37, 95% CI 0.01 to 9.45; P = NS).

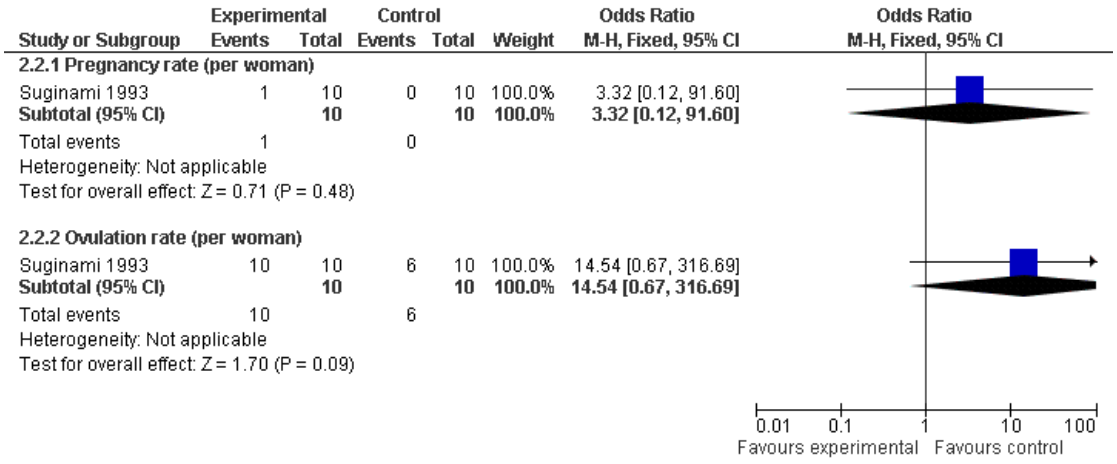
Figure 4. Forest plot of comparison: 2 Anti-oestrogen versus anti-oestrogen, outcome: 2.1 Clomiphene versus tamoxifen.



- Clomiphene (50 mg) plus tamoxifen (20 mg) versus clomiphene (100 mg)

One trial reported on this comparison (Suginami 1993). This was a small trial of 20 participants. There were no significant differences found for pregnancy (OR 3.32, 95% CI 0.12 to 91.60; P = NS) or ovulation rate (OR 14.54, 95% CI 0.67 to 316.69; P = NS) between the two groups (refer to Figure 5). There were no instances of OHSS in either group and all of the pregnancies were singleton.

Figure 5. Forest plot of comparison: 2 Anti-oestrogen versus anti-oestrogen, outcome: 2.2 Clomiphene plus tamoxifen versus clomiphene.



Anti-oestrogen plus other medical therapy versus anti-oestrogen alone

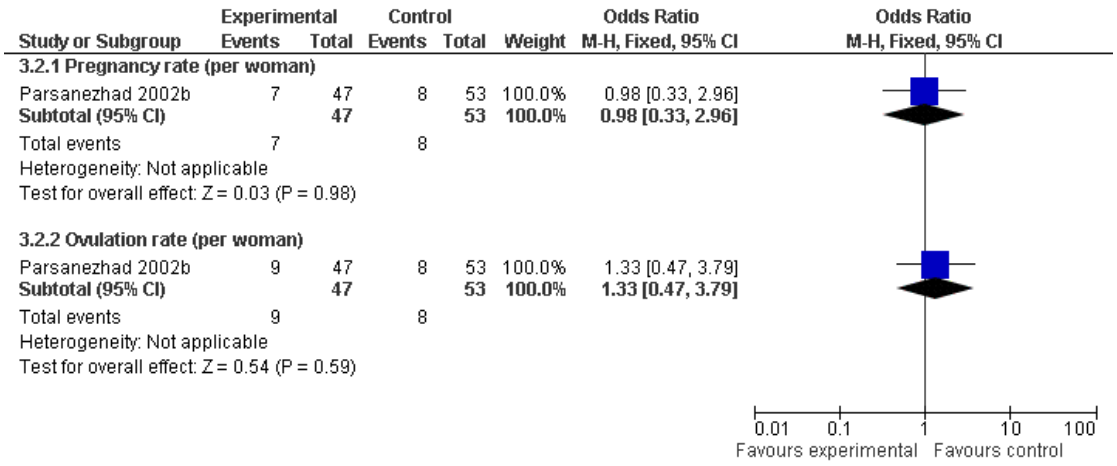
- Clomiphene (up to 150 mg) plus ketoconazole (400 mg) versus clomiphene (up to 150 mg)

One study reported this comparison (Hassan 2001). There was no evidence of a difference between groups for pregnancy rate (OR 2.37, 95% CI 0.88 to 6.40; P = NS) or multiple pregnancy rate (OR 1.18, 95% CI 0.37 to 3.78; P = NS); ovulation rate was presented in a form that precluded analysis. There was one instance of miscarriage or spontaneous abortion in the clomiphene group (OR 0.28, 95% CI 0.01 to 7.08; P = NS).

- Clomiphene (200 mg) plus bromocriptine (7.5 mg) versus clomiphene (200 mg)

One study (Parsanezhad 2002b) reported this comparison. The study did not identify any differences in pregnancy (OR 0.98, 95% CI 0.33 to 2.96; P = NS) or ovulation rate (OR 1.33, 95% CI 0.47 to 3.79; P = NS) between the two groups. No other outcomes were reported (Figure 6).

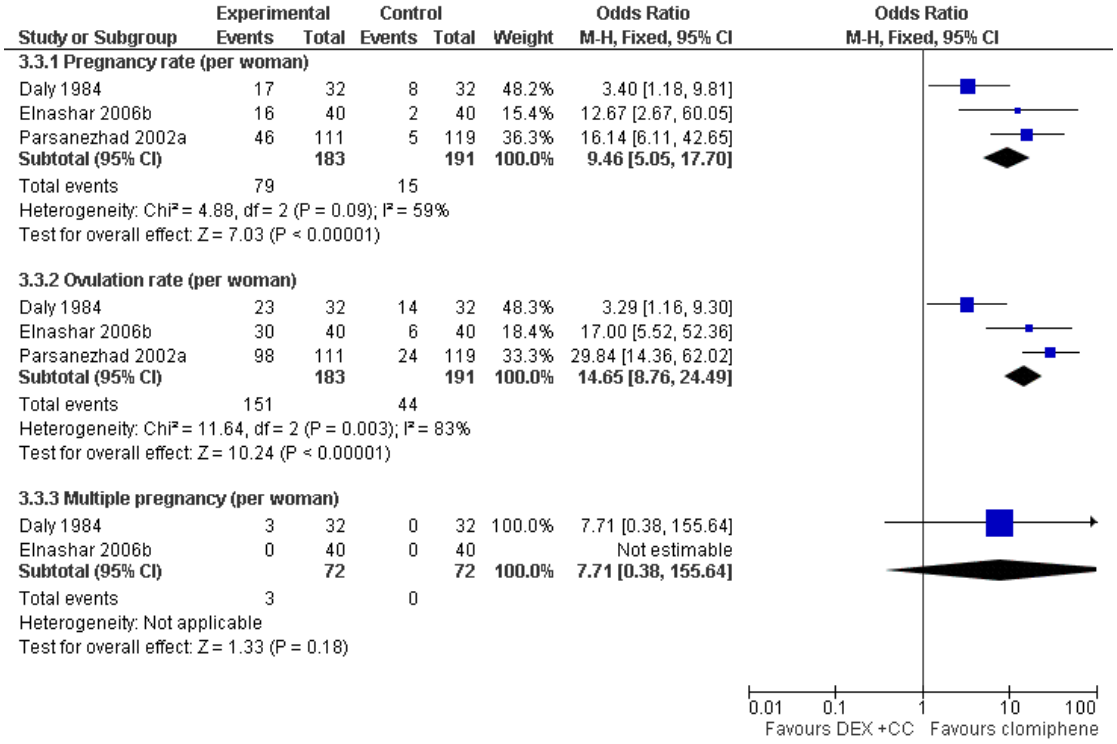
Figure 6. Forest plot of comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, outcome: 3.2 Clomiphene plus bromocriptine versus clomiphene.



- Clomiphene (50 to 200 mg) plus dexamethasone (0.5 to 2.0 mg) versus clomiphene (50 to 200 mg)

Three studies reported on this comparison (Daly 1984; Elnashar 2006b; Parsanezhad 2002a). Analysis of the pregnancy rate showed a large and consistent benefit of clomiphene plus dexamethasone (Figure 7) (fixed OR 9.46, 95% CI 5.05 to 17.7; I^2 59%, P < 0.00001). Ovulation rate had an I^2 of 83%. When the studies were examined further the dosage of dexamethasone prescribed was 0.5 mg in the study by Daly 1984 and 2 mg in the remaining studies. If Daly 1984 was excluded from the analysis the I^2 = 0% and the OR was 25.3 (95% CI 13.7 to - 46.6; P < 0.00001) in favour of clomiphene plus dexamethasone. There was no significant difference in the incidence of multiple pregnancy per woman (Daly 1984; Elnashar 2006b) (OR 7.71, 95% CI 0.38 to 155.64; P = NS). No side effects were reported by Elnashar 2006b in either group.

Figure 7. Forest plot of comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, outcome: 3.3 Clomiphene plus dexamethasone versus clomiphene.

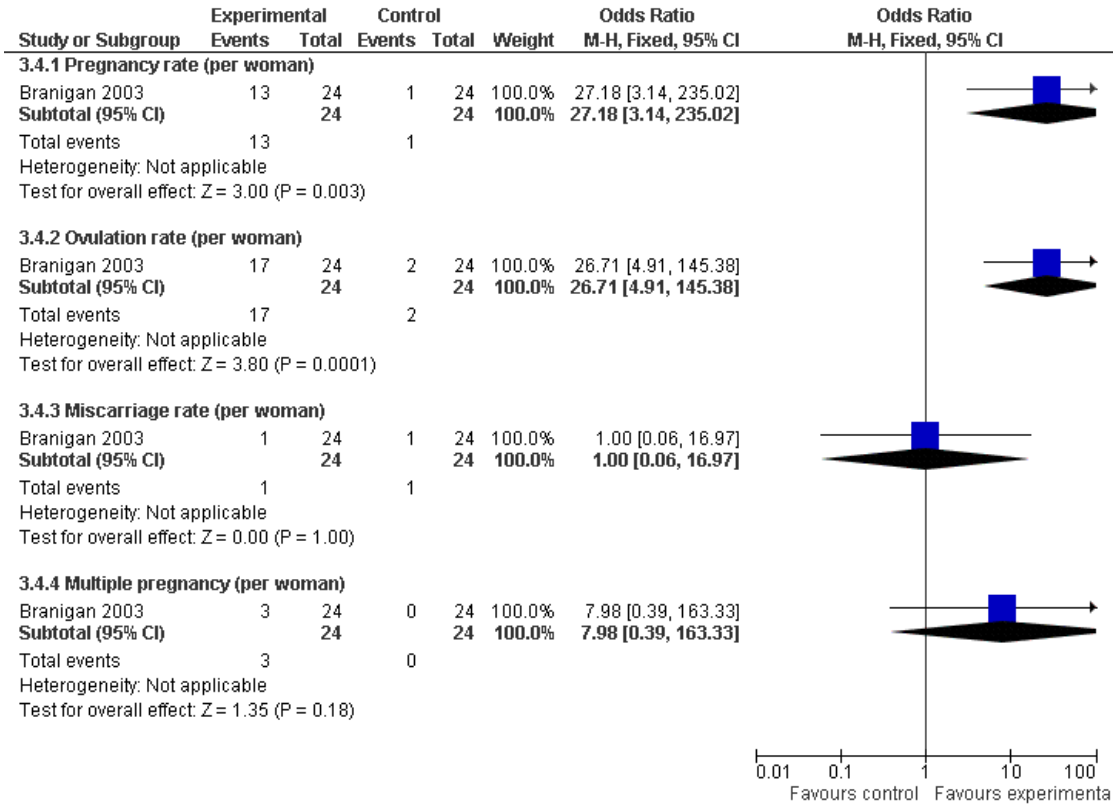


- Clomiphene (100 mg) plus combined oral contraceptive versus clomiphene (100 mg)

One study reported on this comparison (Branigan 2003). Analysis of pregnancy rate (per woman) showed a benefit of clomiphene plus combined oral contraceptive (1 trial, 51 participants; fixed OR 27.18, 95% CI 3.14 to 235.02); the NNT was 2.0 (95% CI

1.4 to 3.4). Ovulation rate (per woman) also showed a benefit in favour of clomiphene plus combined oral contraceptive (1 trial, 51 participants; fixed OR 26.71, 95% CI 4.91 to 145.38); the NNT was 1.6 (95% CI 1.2 to 2.4). There was no evidence of a difference in miscarriage rate (OR 1.0, 95% CI 0.06 to 16.97; P = NS) or multiple pregnancy rate per woman (OR 7.98, 95% CI 0.39 to 163.33; P = NS) between the two groups (Figure 8).

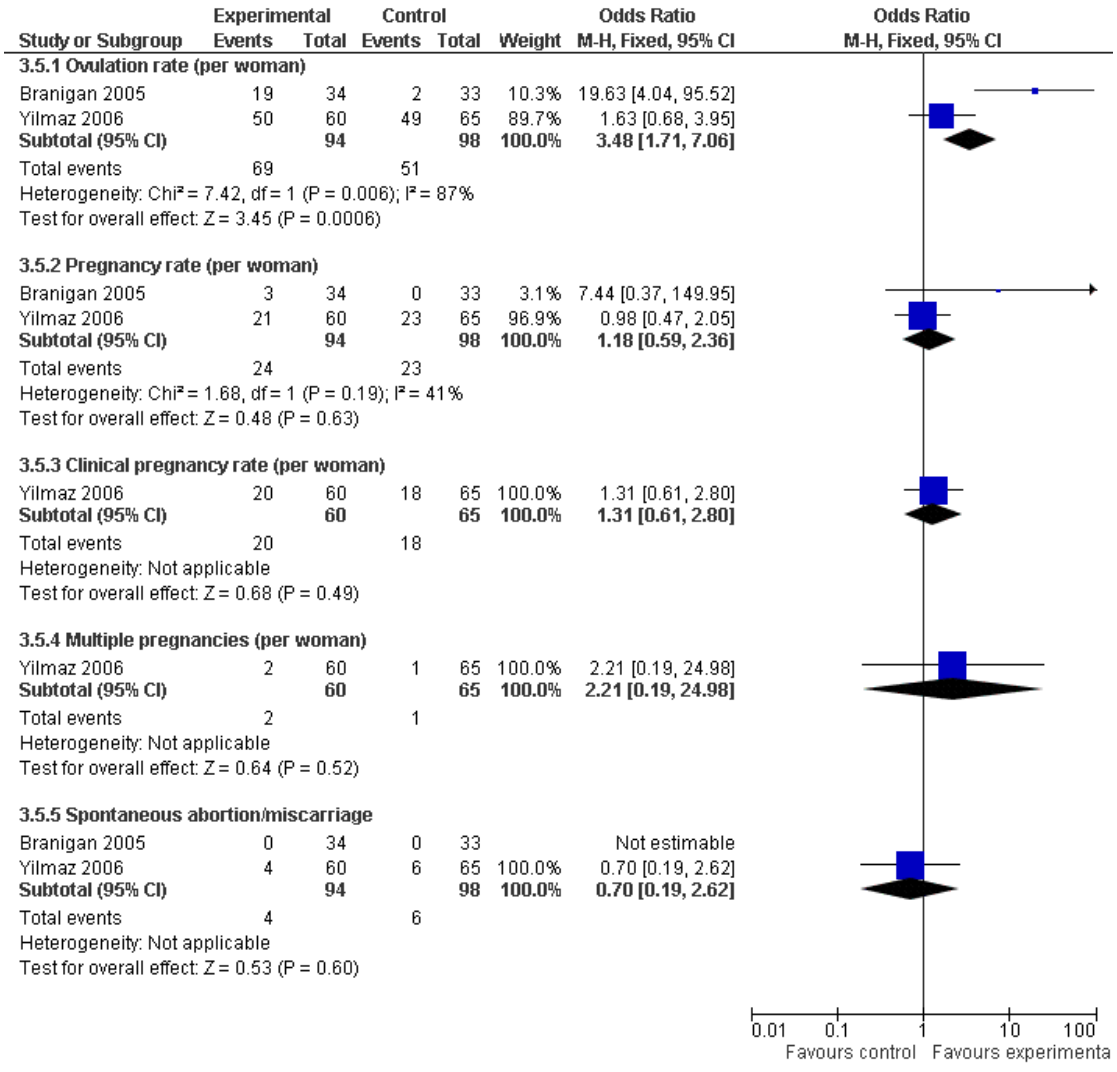
Figure 8. Forest plot of comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, outcome: 3.4 Clomiphene plus combined oral contraceptive vs clomiphene.



- Clomiphene plus hCG versus clomiphene alone

Two studies made this comparison (Branigan 2005; Yilmaz 2006). There were no significant differences in pregnancy rate between the two groups (OR 1.18, 95% CI 0.59 to 2.36; P = NS). Heterogeneity for ovulation rate was high at 87% and this is probably due to the different doses administered in the two trials. Branigan 2005 administered microdose hCG and Yilmaz 2006 administered a dose of 10,000 IU (Figure 9). There was no difference identified in the incidence of spontaneous abortion or miscarriage reported in the two studies (OR 0.70, 95% CI 0.19 to 2.62; P = NS). Only Yilmaz 2006 reported on multiple pregnancies and there was no difference identified between the two groups (OR 2.21, 95% CI 0.19 to 24.98; P = NS).

Figure 9. Forest plot of comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, outcome: 3.5 Clomiphene plus hCG versus clomiphene alone.



- Clomiphene citrate versus clomiphene plus hormone supplementation

One study reported on this comparison (Elkind-Hirsch 2005). This was a study of 65 women. There were no significant differences identified for ovulation rate (OR 1.34, 95% CI 0.42 to 4.27; P = NS), pregnancy rate (OR 0.42, 95% CI 0.07 to 2.48; P = NS) or incidence of adverse events.

Anti-oestrogen plus other medical therapy versus anti-oestrogen plus other medical therapy

No trials were found making this comparison.

DISCUSSION

Clomiphene and placebo or tamoxifen

Analysis of the three trials comparing clomiphene with placebo shows that clomiphene improves ovulation and pregnancy rates. The two trials comparing clomiphene with tamoxifen have shown no evidence of a difference in rates of pregnancy and ovulation between the two drugs. One trial (Boonstanfar 2001) also shows no evidence of a difference for rates of multiple pregnancy, miscarriage and OHSS between drugs. These outcomes all had very low, or zero, event rates and so the single trial lacks the sample size needed to determine a definite answer. No trials were found comparing tamoxifen with placebo so it is merely conjecture that tamoxifen is better than placebo. The recent NICE report (NICE 2004) regarded both clomiphene and tamoxifen as equally effective agents for ovulation induction in anovulatory infertility.

Suginami 1993 studied the effectiveness of clomiphene and tamoxifen combination therapy when compared to clomiphene alone. The trial showed no evidence of a difference between treatments for pregnancy, ovulation or OHSS. However, the trial was very small (20 participants) and probably had an inadequate sample size to prove a difference between groups. Further research is needed.

Clomiphene resistance

Four of the trials were performed on clomiphene-resistant women only (Branigan 2003; Branigan 2005; Parsanezhad 2002a; Parsanezhad 2002b). Rates of clomiphene resistance are approximately 15% to 40% in women with PCOS (Kousta 1997; Pritts 2002; Wolf 2000). Definitions vary with the dose required to define resistance ranging from 150 mg to 250 mg (NICE 2004; Parsanezhad 2002a).

In Hassan 2001 the incidence of clomiphene resistance after ketoconazole pretreatment was 11.6% (5/43) in the treatment group and 32.4% (12/37) in the control group. This is a statistically significant result (fixed OR 0.27, 95% CI 0.09 to 0.87). It is not, however, one of the outcomes assessed in this review. In this trial the difference between the treatment and control groups for the outcome of pregnancy was not statistically significant, a trend toward the treatment group was present though. The trial authors clouded the results by shifting participants who failed to respond to 150 mg clomiphene to hMG treatment. No data were provided on the numbers from each group however it would be reasonable to assume that more participants from the control group, with its higher rates of clomiphene resistance, required this. This, coupled with the low power of the trial, may be the reason for the lack of a significant difference in pregnancy rates.

Dexamethasone as an adjunct

The three trials of this treatment (Daly 1984; Elnashar 2006b; Parsanezhad 2002a) provided good evidence that dexamethasone improved pregnancy rates when used as a medical adjunct to clomiphene.

There was significant heterogeneity between trial designs, one trial included only women who had not received clomiphene while the other included only clomiphene-resistant women. Parsanezhad 2002a also excluded women with raised dehydroepiandrosterone sulphate (DHEAS) levels whereas Daly 1984 reported that the effect of dexamethasone was largest in women with raised DHEAS levels. Human CG was used to trigger ovulation in Parsanezhad 2002a and was not used in Daly 1984 (see below). The dose regimens in the trials were also significantly different. Daly 1984 used 0.5 mg of dexamethasone and Parsanezhad 2002a and Elnashar 2006b used 2.0 mg. It is not possible to state which dose is of most benefit from analysis of these trials. However from Parsanezhad 2002a, which is a larger and better conducted trial, for women with clomiphene resistance using dexamethasone 2.0 mg from day 5 to day 14 of the cycle would seem more appropriate than 0.5 mg, until further data on 0.5 mg are available.

The differences described lead to a large difference between results in the control groups. The results for analysis of ovulation rate are homogenous, with similar ORs and an I^2 value of 0%; greater than 50% has tentatively been described as notable heterogeneity (Higgins 2002). All trials do, however, show a statistically significant result for pregnancy and ovulation rates when considered separately.

Despite this uncertainty in the analysis dexamethasone shows potential as a cheap and non-invasive treatment option for women

with PCOS, perhaps especially those that have failed to respond to standard therapy. Further large RCTs are required.

Bromocriptine as an adjunct

Bromocriptine for ovulation induction has been shown to have value in hyperprolactinaemic women (Franks 1979). In the Parsanezhad 2002b trial no evidence of an effect on ovulation or pregnancy rate was shown with bromocriptine as an adjunct to clomiphene when compared with placebo, however only 100 women were studied.

CYP17a inhibitors

As noted above the Hassan 2001 trial did not provide evidence of a statistically significant benefit to pregnancy rates per woman by addition of ketoconazole to clomiphene therapy.

Combined oral contraceptives (COCs) and hormone supplementation

The suggested mode of action of COCs is suppression of the hypothalamic-pituitary-ovarian axis. This leads to suppression of androgens, 17ß-estradiol and LH levels in the early follicular phase. This improved milieu interieur may increase the ovarian response to clomiphene. The authors of Branigan 2003 believed that the androgen level may be the significant factor as those women who failed to ovulate in the treatment group had persistently high levels of androgens. This fits with the proposed mechanism of action of other ovulation induction agents.

The single trial (Branigan 2003) on this adjunct to clomiphene therapy found evidence that COCs considerably improve ovulation and pregnancy rates. This trial had an unusual protocol which withdrew clomiphene treatment from those women who did not ovulate in the first cycle. It was also a small trial (48 participants) and had correspondingly wide confidence intervals. In addition, the use of progestin therapy to induce menstruation before clomiphene administration was not performed in the control arm and prescription of progestins prior to clomiphene is a common albeit unstudied practice. The NNT for ovulation was 1.6 and for pregnancy it was 2.0. COCs, like dexamethasone, may have potential as a cheap, safe and effective adjunct in women who have been shown to be resistant to standard therapy. Further, more rigorous RCTs are required.

Only one study reported the use of hormone supplementation as an adjunct (Elkind-Hirsch 2005) and there was no evidence of any additional benefits with its usage.

Human chorionic gonadotrophin (hCG)

The use of hCG may have an impact on the number of women ovulating and hence possibly on the pregnancy rate. The only comparison to have one trial reporting the use of hCG and one trial not reporting the use of hCG was clomiphene plus dexamethasone versus clomiphene. As discussed above these trials are heterogenous in design in several aspects and conclusions on the effectiveness of hCG cannot be drawn from these trials.

Limitations of the review

All of the trials included in this review have methodological flaws, which weakens the results found. More rigorous RCTs are required for all the interventions.

Live birth rate is the gold standard primary outcome for RCTs of this nature (Vail 2003). Only one of the trials (Boonstanfar 2001) reported this. Using pregnancy rate as a surrogate endpoint is of dubious accuracy. Other poorly reported outcomes were miscarriage, multiple pregnancy, women reported adverse effects and incidence of OHSS. Miscarriage is an important outcome, particularly in women with PCOS where there is an increased risk of complications of pregnancy. The failure of the trials to follow up to live birth and report miscarriage rate is significant given the concerns of an increased risk when using these agents. Multiple pregnancy rates in medically assisted conception are often high and trials should ideally have enough power to identify an effect. OHSS is a rare but potentially life-threatening complication of ovulation induction therapy; it is an important outcome but if it did not occur in the trial populations it may not have been mentioned. Ideally OHSS should be mentioned, even as a negative.

The effectiveness of these drugs in different subgroups of women has not been proven for any of the interventions under review. Four of the trials were on women with PCOS only. The other eight trials, those performed on clomiphene and tamoxifen, did not differentiate between most causes of anovulation. There may be a difference in efficacy between aetiologies. The new consensus definition of PCOS (ESHRE/ASRM 2003) is wider than the definitions used in the past and it is likely (due to the prevalence of PCOS) that the majority of the participants in the seven non-specific trials would now be considered as having PCOS. Trials should ideally be performed on women with a specific aetiology, or have results separated by aetiology.

It is possible that some participants may have had a cause of anovulation other than that specified by the WHO group 2 classification, especially in the older included trials. Outcomes may be different between WHO groups and so this may be a source of error.

Sensitvity analysis

Sensitivity analysis was unable to be conducted due the lack of studies available in each comparison for the primary outcome of live birth.

AUTHORS' CONCLUSIONS

Implications for practice

Strong evidence in favour of one anti-oestrogen or adjunctive agent has not been found. This review shows evidence supporting the

effectiveness of the current first-line treatment, clomiphene citrate, in terms of pregnancies. There is no evidence of a difference in effect between clomiphene and tamoxifen or clomiphene alone but the number of women studied is too small to be conclusive. No trials comparing tamoxifen and placebo could be found. There are insufficient data to determine the place of ketoconazole, tamoxifen, bromocriptine, hCG or hormone supplementation as an adjunct with clomiphene versus clomiphene alone in anovulatory, normoprolactinaemic women. Further trials are clearly needed in these areas. Dexamethasone and COCs appear to be promising adjuncts to clomiphene treatment and also require further research.

Implications for research

Clomiphene is now widely accepted as an effective treatment and further trials against placebo are unlikely to be conducted. Large, well designed RCTs are needed in both the long-standing interventions such as clomiphene, the medical adjunctive drugs and the newer drugs such as aromatase inhibitors. Trials comparing against placebo and between interventions and adjuncts are needed. This review shows that trials currently available are often of poor quality and have potentially serious flaws, primarily due to lack of data on live birth.

Differentiation between results by aetiology of anovulation is also needed in subsequent trials. RCTs should follow the consolidated standards of reporting trials (CONSORT) guidelines (Moher 2001). Trials should be of sufficient duration to have live birth as their primary outcome and should ideally report all secondary outcomes listed in this review, in particular incidence of multiple pregnancy and miscarriage. All rates should be reported per woman, not per cycle, and in actual numbers of participants not percentages.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boonstanfar 2001

Methods	Method of allocation and randomisation: Randomised, computer-generated random number table via opaque envelopes Blinding: No Number of centres: Not stated Design: Parallel Power calculation: Not stated Number of women randomised: 95 to 47 to CC and 48 to TMX Number of women analysed: 86 Number of withdrawals and reasons: nine, did not return for follow up Intention to treat analysis: No Source of funding: Not stated
Participants	Inclusion criteria: Anovulation with no other cause of infertility Age: CC 26.5±4.3, TMX 26.6±4.3 Duration of infertility: CC 3.7±2.5 years, TMX 3.5±2.9 years Source of women: Not stated Exclusion criteria: Uterine or adnexal pathology, abnormal hSG, abnormal semen analysis, age >40 years, hyperprolactinaemia, hypo- or hyperthyroidism, FSH >20 mIU/ml, progesterone >3.0ng/ml, previous exposure to ovulation induction agents, hepatic or renal disease, presence of a contraindication to trial drugs Location: Los Angeles, USA
Interventions	Treatment(s): Both groups had a progesterone induced withdrawal bleed and then either 50mg CC on days five to nine, increased to 100mg and then 150mg if participant remained anovulatory; or 20mg TMX on days five to nine, increased to 40mg and then 60mg if participant remained anovulatory Control or placebo: None Duration: Not stated
Outcomes	Relevant outcomes: Live birth (incomplete follow up), pregnancy, ovulation, miscarriage (no definition), multiple birth, OHSS and women reported adverse effects
Notes	Contacted authors re: power calculation, blinding, funding and ongoing pregnancy results; no reply received

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random number table
Allocation concealment?	Yes	Adequate

Boonstanfar 2001 (*Continued*)

Blinding? All outcomes	No	None
Incomplete outcome data addressed? All outcomes	Unclear	All women accounted for
Free of selective reporting?	Unclear	All stated outcomes reported on

Branigan 2003

Methods	Method of allocation and randomisation: Pre-randomised schedule Blinding: Unclear Number of centres: Not stated Design: Parallel Power calculation: yes Number of women randomised: 48 Number of women analysed: 48 Number of withdrawals and reasons: Intention-to-treat analysis: Yes Source of funding: Not stated
Participants	Inclusion criteria: Anovulation while receiving ≥150 mg clomiphene, under 36 years old, tubal patency (HSG/laparoscopy), normal fasting glucose and insulin, normal prolactin, thyroid stimulating hormone and FSH levels, DHEAS ≤200 ug/ml, norm oestrogenic, no contraindication to COC use and partner with normal semen analysis. Age: 28.2±3.4 Duration of infertility: 2.4±0.8 Source of women: Private tertiary infertility clinic Exclusion criteria: Not stated Location: Bellingham, USA
Interventions	Treatment(s): COC (Desogen, 0.03mg ethinyl estradiol and 0.15mg desogestrel) continuously for 42 to 50 days followed by one cycle of 100mg CC (days 5-9); 10,000 U hCG ovulation trigger Control/Placebo: 38-56 days no treatment followed by one cycle of 100 mg CC (days 5-9); 10,000 U hCG ovulation trigger Duration: Up to 6 cycles of CC for those women who ovulated but did not become pregnant in the first cycle
Outcomes	Relevant outcomes: Ovulation, pregnancy, multiple pregnancy, miscarriage (no definition)
Notes	Contacted authors re: randomisation and allocation concealment, treatment protocol, adverse effects and definitions used; no reply received
Risk of bias	

Branigan 2003 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised permuted blocks of four
Allocation concealment?	Unclear	Adequate - opaque envelopes
Blinding? All outcomes	Unclear	Unclear
Incomplete outcome data addressed? All outcomes	No	All women randomised analysed. No report of live birth
Free of selective reporting?	No	Unclear

Branigan 2005

Methods	Method of allocation and randomisation: Randomised parallel two arm study. Random permuted blocks with a block size of four used to generate the 2 groups. Consecutively numbered opaque envelopes contained the group assignment which was opened after the women was enrolled in the study Blinding: No blinding Number of centres: Design: Parallel Power calculation: Yes, based on expected ovulation rate Number of women randomised: 70 Number of women analysed: 67 Number of withdrawals and reasons:1 women in CC+hCG and 3 in the 150mg CC group did not begin the study Intention-to-treat analysis: All women who received a treatment were analysed (n=67) Source of funding: Not stated
Participants	Inclusion criteria: Previously documented dominant follicle or follicles >/12mm mean diameter on transvaginal ultrasound follicular monitoring while receiving CC at the 100mg dose but failed to ovulate; under the age of 40 years; have documented normal uterine cavity and patent tubes by either hysterosalpingogram or laparoscopy and hysteroscopy; have normal fasting glucose and insulin levels, normal prolactin, thyroid stimulating hormone and FSH and dehydroepiandrosterone sulphate levels of 200 μg/ml or less. The male partner was to have normal semen analysis according to WHO criteria Age: mean age of CC+hCG group was 34.1±1.1 years, the mean age of CC only was 33.4±1.3 years Duration of infertility: No details Source of women: Private tertiary infertility clinic Exclusion criteria: Not stated Location: USA

Branigan 2005 (*Continued*)

Interventions	Transvaginal ultrasound follicular monitoring started on day 12 and repeated every 1-2 days until mean diameter of lead follicle was greater than 20mm Treatment(s): CC+hCG; CC 100mg on days 5-9 + daily IM injections of 200IU of hCG when the lead follicle was 12mm or larger until 20mm or larger was attained (If the follicle diameter failed to increase by more than 1mm per day after 14 mm or 14 mm was not achieved monitoring was ceased and the cycle cancelled) (n=35) Control or placebo: CC only 150mg days 5-9 (n=35) Both groups received 10,000 IU hCG IM injection when lead follicle diameter was 20mm or greater Timed intercourse advised on day of hCG injection and following day Duration: One cycle
Outcomes	Relevant outcomes: Ovulation rate, endometrial thickness, number of follicles, E2 levels, testosterone levels, P4 levels, pregnancy rate
Notes	Pregnancy confirmed by serum hCG and 7 week gestational ultrasound. BMI group 1: 21.3±0.4, group 2: 21.2±0.3

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random permuted blocks with a block size of four used to generate the 2 groups
Allocation concealment?	Yes	Consecutively numbered opaque envelopes contained the group assignment which was opened after the women was enrolled in the study
Blinding? All outcomes	No	No blinding
Incomplete outcome data addressed? All outcomes	No	Number of women randomised: 70 Number of women analysed: 67 Number of withdrawals and reasons:1 women in CC+hCG and 3 in the 150mg CC group did not begin the study No details of adverse events, no report of live birth
Free of selective reporting?	No	Results section reported on additional relevant outcomes to those stated in the methods section

Cudmore 1966

Methods	Method of allocation and randomisation: Entered group by chance, cross-over trial Blinding: Double blind Number of centres: Not stated Design: Parallel Power calculation: Not stated Number of women randomised: 22 Number of women analysed: 22 Number of withdrawals and reasons: NA Intention to treat analysis: Yes Source of funding: Support and drug supplied by Wm S Merrell Company, Cincinnati, Ohio
Participants	Inclusion criteria: All women stated as anovulatory. Secondary amenorrhoea (>2 years) or oligomenorrhoea (no more than 4 periods a year and none in the 3 months prior to study) or anovulatory infertility (>2 years). Plus no infertility treatment in the three months prior to the study. Plus no other cause of infertility found. Age: Treatment: 18 to 33, placebo: 20 to 29 Duration of infertility: Not stated Source of women: Not stated Exclusion criteria: Not stated Location: Halifax, Canada
Interventions	Treatment(s): 50mg CC (days 1-14) (n=13) Control or ppPlacebo: Placebo (days 1-14) (n=9) Duration: 3 cycles then 3 cycles
Outcomes	Relevant outcomes: Ovulation and women reported adverse effects, hormonal responses
Notes	Authors not contacted as trial published >15 years ago

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Entered treatment group by chance
Allocation concealment?	Unclear	Unclear - coded but not clear if this was centrally administered
Blinding? All outcomes	Unclear	Double blind
Incomplete outcome data addressed? All outcomes	No	All women accounted for No adverse events for miscarriage reported, no report of live birth
Free of selective reporting?	No	Pregnancy not noted as an outcome in methods but described in results

Daly 1984

Methods	Method of allocation and randomisation: Pre-randomised schedule Blinding: Unclear Number of centres: Not stated Design: Parallel Power calculation: Not stated Number of women randomised: 64 Number of women analysed: 45 Number of withdrawals and reasons: 9 discontinued in 1st cycle, 10 excluded due to other infertility factors Intention to treat analysis: Yes Source of funding: Not stated
Participants	Inclusion criteria: Either anovulatory as evidenced by basal body temperature charting or oligomenorrhoeic but responsive to progesterone. No previous exposure to clomiphene Age: Not stated Duration of infertility: Not stated Source of women: Not stated Exclusion criteria: Hyperprolactinaemia, hyper- or hypothyroidism, major male factor, tubal disease (hSG) Location: USA
Interventions	Treatment(s): 50mg CC (days 5-9) plus 0.5mg DEX. CC increased up to 150mg if participant remained anovulatory. women remaining anovulatory at 150mg crossed to other arm of trial, as did women who ovulated but had an abnormal post-coital test or endometrial biopsy Control/Placebo: 50mg CC (days 5-9). CC increased up to 150mg if participant remained anovulatory. women remaining anovulatory at 150mg crossed to other arm of trial, as did women who ovulated but had an abnormal post-coital test or endometrial biopsy Timed intercourse: No details Duration: Not stated
Outcomes	Relevant outcomes: Ovulation, pregnancy
Notes	Authors not contacted as trial published >15 years ago

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Pre-randomised schedule
Allocation concealment?	No	Unclear
Blinding? All outcomes	No	No details
Incomplete outcome data addressed? All outcomes	No	Nine women (four CC, five CC+DEX) discontinued in the first cycle and ten women

Daly 1984 (*Continued*)

		were found to have other infertility factors leaving 22 women receiving CC alone and 23 receiving CC+DEX No details of adverse events, no report of live birth
Free of selective reporting?	No	No outcome measures were reported in the methods section

Elkind-Hirsch 2005

Methods	Method of allocation and randomisation: randomised Blinding: No, open-label study Number of centres: one Design: Parallel Power calculation: Yes, based on pregnancy rate Number of patients randomised: 71 Number of women analysed: 65 Number of withdrawals and reasons: Abnormal scans and no treatment received Intention to treat analysis: Yes for women with a P assay Source of funding: Grant from Columbia Laboratories Inc
Participants	Inclusion criteria: Aged 21 to 35 years, oligo amenorrhoea, BMI >18 and <38. Age: Median age 28 Duration of infertility: Not stated Source of women: Womens Health Research Institute (April 2003 - July 2004) Exclusion criteria: Pregnant, known endometrial or uterine anomaly, tubal occlusion, previously failed to ovulate in response to clomiphene. Premature ovulation failure Location: USA
Interventions	Treatment(s): Clomiphene citrate (100mg orally for five days from days three to seven of the cycle) Control or placebo: Clomiphene Citrate (100mg orally for five days from days three to seven of the cycle)+HS in the form of estradiol (E2) 1.5mg (two tablets) PO BID on cycle day 8. On cycle day ten, women commenced monitoring urine LH levels. E2 was discontinued with detection of LH surge If woman was pregnant vaginal progesterone administered daily for additional 10 weeks Timed intercourse: encouraged from cycle day ten Duration: one cycle
Outcomes	Relevant outcomes: Pregnancy rate, ovulation rate
Notes	Pregnancy assessed as serum hCG two weeks following LH surge Power calculation indicated 458 women per group should be randomised. Study stopped after 88 participants
Risk of bias	

Elkind-Hirsch 2005 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised, no details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	No	Open-label study
Incomplete outcome data addressed? All outcomes	No	Six women had an abnormal scan and were discontinued without receiving treatment No details of adverse events, no report of live birth
Free of selective reporting?	No	No details of adverse events, no report of live birth

Elnashar 2006b

Methods	Method of allocation and randomisation: Randomised placebo-controlled study Blinding: Yes, women and clinician Number of centres: one Design: Parallel Power calculation: Yes, based on results of study by Parsanezhad 2002a; Parsanezhad 2002b Number of women randomised: 80 Number of women analysed: 80 Number of withdrawals and reasons: 0 Intention-to-treat analysis: All women randomised were analysed Source of funding: Not stated
Participants	All women had PCOS as defined by Rotterdam criteria, not having hyperprolactinaemia, clinical evidence of hypercortism or thyroid dysfunction Inclusion criteria: Aged 18 to 39 years, period of infertility > two years, serum DHEAS within normal levels, no treatment taken during previous two months Age:CC+DEX 23.4±3.6 years, CC+placebo 25.2±2.4 years Duration of infertility: CC+DEX 2.1±0.9 years, CC+placebo 3.2±1.4 years Source of women: Outwomen hospital clinic (March 2004-December 2004) Exclusion criteria: History of pelvic surgery or infertilty factor other than anovulation Location: Eygpt
Interventions	Induction of menses using P-in-oil (100mg); 10,000 IU IM hCG given when at least one follicle >18mm Treatment(s): Clomiphene citrate 100mg daily from days 3 to 7 + DEX 2mg daily PO in two divided doses from days 3 to 12 Control or placebo: Clomiphene citrate 100mg daily from days 3 to 7 + placebo (folic acid) from days 3 to 12 Timed intercourse advised 24-36 hours after hCG

Elnashar 2006b (*Continued*)

	Duration: One cycle
Outcomes	Relevant outcomes: Ovulation rate, number of follicles >18mm, endometrial thickness and pregnancy rate
Notes	All women had previously received clomiphene and were defined as clomiphene resistant Clinical pregnancy defined as presence of gestational sac on USS 1 week after missed period

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Assigned randomly, no further details
Allocation concealment?	Unclear	Used closed dark envelopes and allocated by a third party (nurse)
Blinding? All outcomes	Yes	Women and physician monitoring cycles were blinded to treatment
Incomplete outcome data addressed? All outcomes	No	All women randomised were analysed, no drop outs, no details of adverse events, no report of live birth
Free of selective reporting?	No	No report of live birth

Garcia 1985

Methods	Method of allocation and randomisation: Random, method not stated Blinding: Double Number of centres: Not stated Design: Crossover Power calculation: Not stated Number of women randomised: 49, 24 to CC and 22 to placebo Number of women analysed: 46 Number of withdrawals and reasons: 21, 11 with difficulty with protocol, 4 with ambivalence towards pregnancy at time, 4 with medical difficulties and 2 left the country Intention-to-treat analysis: Yes Source of funding: National Institute of Child Health and Human Development grant Notes: Cross-over trial, phase 1 data only
Participants	Inclusion criteria: Amenorrhoea (>6 months), progesterone withdrawal bleeding and no other known cause of infertility Age: Mean 27.6 years Duration of infertility: Not stated Source of women: Dept of Obstetrics and Gynecology Exclusion criteria: Not stated

Garcia 1985 (*Continued*)

	Location: Philadelphia, USA
Interventions	Treatment(s): 50 mg clomiphene, increased by 50mg if ovulation failed to occur, up to 250 mg Control or placebo: Placebo, 1 tablet, increased up to 5 tablets similar to treatment Duration: 5 cycles then 5 cycles
Outcomes	Relevant outcomes: Ovulation and pregnancy
Notes	Authors not contacted as trial published >15 years ago

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not stated
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Yes	Double blind, no details
Incomplete outcome data addressed? All outcomes	No	49 randomised and 46 analysed (21 withdrawals; 11 with difficulty with protocol, 4 with ambivalence towards pregnancy at time, 4 with medical difficulties and 2 left the country) No details of adverse events, no report of live birth
Free of selective reporting?	No	No details of adverse events, no report of live birth

Hassan 2001

Methods	Method of allocation and randomisation: Random number table Blinding: No Number of centres: 1 Design: Parallel Power calculation: Not stated Number of women randomised: 97, 49 to treatment and 48 to control Number of women analysed: 80, treatment 43 and control 37 Number of withdrawals and reasons: Control 11, treatment 6, reasons not stated Intention-to-treat analysis: Not stated Source of funding: Not stated
Participants	Inclusion criteria: Infertile women with PCOS and insulin resistance Age: Not stated

Hassan 2001 (*Continued*)

	Duration of infertility: Not stated Source of women: Not stated Exclusion criteria: Male factor infertility Location: Alexandria, Egypt
Interventions	Treatment(s): Ketoconazole 400mg for 85 days pretreatment followed by CC 100 to150mg, women persistently failing to ovulate on 150mg CC were shifted to hMG Control/Placebo: CC 100-150mg, women persistently failing to ovulate on 150mg CC were shifted to hMG Duration: 3-6 cycles
Outcomes	Relevant outcomes: Pregnancy, multiple pregnancy, spontaneous abortion (after cord pulse)
Notes	Authors contacted re: power calculation, allocation concealment, blinding, inclusion and exclusion criteria, exclusions and drop outs, age ranges, ITT analysis, hMG treatment, outcome definitions and side effects; no reply received Incidence of clomiphene resistance - treatment 11.6% (5/43), control 32.4% (12/37)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomly divided using random number table
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	No blinding
Incomplete outcome data addressed? All outcomes	No	Number of women analysed: 80, treatment 43 and control 37 Number of withdrawals and reasons: Control 11, treatment 6, reasons not stated No details of adverse events, no report of live birth
Free of selective reporting?	No	Pregnancy and multiple pregnancy as outcomes are not described in the methods section, similarly with anti-oestrogenic markers

Johnson 1966

Methods	Method of allocation and randomisation: Random, pharmacy coded drug boxes Blinding: Double Number of centres: 5 Design: Cross-over Power calculation: Not stated Number of women randomised: 78, 33 to CC and 32 to placebo Number of women analysed: 65 Number of withdrawals and reasons: 13, 8 failed to return or did not comply with protocol and 5 became pregnant in the first phase Intention-to-treat analysis: Not stated Source of funding: supported by Wm S Merrell Company, Cincinatti, Ohio. Notes: Cross-over trial, phase-1 data only
Participants	Inclusion criteria: Anovulation for >6 months, adequate endogenous oestrogen, no local or systematic defect that may interfere with CC action Age: Not stated Duration of infertility: Not stated Source of women: Not stated Exclusion criteria: Not stated Location: USA
Interventions	Treatment(s): 100mg CC days 6-10 Control or placebo: Placebo days 6-10 Duration: 1 cycle then 1 cycle
Outcomes	Relevant Outcomes: Pregnancy and ovulation
Notes	Contact authors? No, trial published >15 years ago

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	No	Coded packages but not clear if source central
Blinding? All outcomes	Unclear	Double blind; no details
Incomplete outcome data addressed? All outcomes	No	All women accounted for; no details of adverse events, no report of live birth
Free of selective reporting?	No	No details of adverse events, no report of live birth

Parsanezhad 2002a

Methods	Method of allocation and randomisation: 3rd party, odd-even numbers given to treatment or control (no further explanation given by authors) Blinding: Double Number of centres: Not stated Design: Parallel Power calculation: Not stated Number of women randomised: 230, 111 to treatment and 119 to control Number of women analysed: Not stated Number of withdrawals and reasons: Not stated Intention to treat analysis: Not stated Source of funding: Not stated
Participants	Inclusion criteria: PCOS as defined by a history of oligo- or amenorrhoea, increased basal LH and androgen levels, polycystic ovaries found on ultrasound. Plus clomiphene citrate resistance, defined as failure to ovulate and achieve normal luteal phase with 250mg dose of CC for five days and at least five cycles Age: Mean age treatment group 23.56 years, control group 23.36 years. Range 19 to 35 for both groups Duration of infertility: Treatment mean 4 years, range 2-14; control mean 4.25 years, range 3-14.5 Source of women: Reproductive and endocrinology division, university Exclusion criteria: Not stated Location: Shiraz, Iran
Interventions	Treatment(s): 200mg CC (days 5-9), 2mg dexamethasone (days 5-14), hCG (10,000U) as an ovulation trigger Control or placebo: 200mg CC (days 5-9), placebo QDS (days 5-14), hCG (10,000U) as an ovulation trigger Duration: Up to 6 cycles
Outcomes	Relevant outcomes: Ovulation rate (%, treatment 88% per women versus control 20% per women; calculated as 98/111 versus 24/119), pregnancy
Notes	Authors contacted re: Power calculation, randomisation, blinding, exclusion criteria, exclusions and drop outs and ITT analysis; no reply received

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	No	Unclear 3rd party (pharmacist), odd-even numbers given to treatment or control (no further explanation given by authors)
Blinding? All outcomes	Unclear	Double blind but no details

Parsanezhad 2002a (*Continued*)

Incomplete outcome data addressed? All outcomes	No	Follow up not clear; no details of adverse events, no report of live birth
Free of selective reporting?	No	No details of adverse events, no report of live birth

Parsanezhad 2002b

Methods	Method of allocation and randomisation: 3rd party (pharmacist), odd-even numbers given to treatment or control (no further explanation given by authors) Blinding: Double Number of centres: 1 Design: Parallel Power calculation: Not stated Number of women randomised: 100, 47 to treatment and 53 to control. Number of women analysed: Not stated Number of withdrawals and reasons: Not stated Intention to treat analysis: Not stated Source of funding: Not stated
Participants	Inclusion criteria: PCOS as defined by women with 3 of the following: infertility, oligo- or amenorrhoea, acne or hirsutism, obesity, increased testosterone, increased DHEAS, LH/FSH ratio >2, polycystic ovaries on ultrasound. Plus clomiphene citrate resistance, defined as failure to ovulate and achieve normal luteal phase with the highest dose of CC for five days and at least five cycles. Plus normal prolactin (80-500mIU/ml). Age: Mean age treatment group 25.02±2.7 years, control group 24.87±2.9 years Duration of infertility: Treatment mean 4.53±3.1 years, range 2 to 22; control 4.02±1.9 years, range 2 to 10 Source of women: Not stated Exclusion criteria: Not stated Location: Shiraz, Iran
Interventions	Treatment(s): 200mg CC on days 5-9, bromocriptine gradual dose increase up to 2.5mg TDS continuously, hCG (10,000U) as an ovulation trigger on day 16 or 17 Control or placebo: 200mg CC on days 5-9, placebo TDS continuously, hCG (10,000U) as an ovulation trigger on day 16 or 17 Duration: Up to 6 cycles
Outcomes	Relevant outcomes: Ovulation rate (%, treatment 18.3% per women versus control 14.9% per women, calculated as 9/47 versus 8/53), pregnancy, women reported adverse effects
Notes	Authors contacted re: Power calculation, randomisation, blinding, exclusion criteria, exclusions and drop outs and ITT analysis; no reply received

Risk of bias

Item	**Authors' judgement**	**Description**

Parsanezhad 2002b (*Continued*)

Adequate sequence generation?	Unclear	Unclear, no details
Allocation concealment?	No	Unclear, 3rd party (pharmacist), odd-even numbers given to treatment or control (no further explanation given by authors)
Blinding? All outcomes	Unclear	Double blind but no details
Incomplete outcome data addressed? All outcomes	No	Follow up data not clear; no details of adverse events such as miscarriage, no report of live birth
Free of selective reporting?	No	No details of adverse events such as miscarriage, no report of live birth

Suginami 1993

Methods	Method of allocation and randomisation: Random, cross-over trial, method not stated Blinding: No Number of centres: Not stated Design: Crossover Power calculation: Not stated Number of women randomised: 20 - 10 to CC plus TMX and 10 to CC Number of women analysed: 20 Number of withdrawals and reasons: 0 Intention to treat analysis: No Source of funding: Not stated Notes: Cross-over trial, phase-1 data only
Participants	Inclusion criteria: Anovulation, normoprolactinaemic Age: Gp A - 29.3±3.1, gp B - 28.6±3.0 Duration of infertility: Not stated Source of women: Not stated Exclusion criteria: None stated Location: Ehime, Japan
Interventions	Treatment(s): Both groups received combination pill (0.05mg ethinyl E2 and 0.5mg norgestrel) to induce withdrawal bleed then Gp A - 100mg CC on days 5-9 for 3 cycles and then 50mg CC plus 20mg TMX on days 5-9 for 3 cycles. Gp B - reverse sequence, otherwise identical Control or placebo: None Timed intercourse - normal intercourse encouraged, no details Duration: 3 cycles then 3 cycles
Outcomes	Relevant outcomes: Ovulation, pregnancy and women reported adverse effects
Notes	Unable to contact authors

Suginami 1993 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	No blinding
Incomplete outcome data addressed? All outcomes	No	No drop outs all women randomised were analysed; no details of adverse events such as miscarriage, no report of live birth
Free of selective reporting?	No	No details of adverse events such as miscarriage, no report of live birth

Vegetti 1999

Methods	Method of allocation and randomisation: Random, method not stated Blinding: Unclear Number of centres: Not stated Design: Parallel Power calculation: Not stated Number of women randomised: 95 - 50 to CC and 45 to TMX Number of women analysed: 95 Number of withdrawals and reasons: Not stated Intention to treat analysis: Not stated Source of funding: Not stated Notes: Abstract only
Participants	Inclusion criteria: Normogonadotrophic anovulation, infertility for >1 year, tubal patency shown by HSG or laparoscopy, normal semen analysis Age: Not stated Duration of infertility: Not stated Source of women: Tertiary infertility centre Exclusion criteria: Not stated Location: Milan, Italy
Interventions	Treatment(s): 100mg CC on days 3-7, if participant remained anovulatory for two cycles then dose doubled or 20mg TMX on days 3-7, if participant remained anovulatory for two cycles then dose doubled Control or placebo: None Duration: Not stated
Outcomes	Relevant outcomes: Ovulation (per cycle, CC 108/129, TMX 92/133), pregnancy and women reported adverse effects

Vegetti 1999 (*Continued*)

Notes	Authors contacted re: Power calculation, random allocation, blinding, reasons for the drop outs, external funding, anovulation definition, exclusion criteria, treatment time limit, ovulation rate per women; no reply received

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Unclear
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	Unclear	Unclear
Incomplete outcome data addressed? All outcomes	No	All women randomised were analysed, no drop outs. No details of adverse events such as miscarriage, no report of live birth
Free of selective reporting?	No	No details of adverse events such as miscarriage, no report of live birth

Yilmaz 2006

Methods	Method of allocation and randomisation: Randomised using random number tables and opaque envelope technique Blinding: Sonographers evaluating follicle size were blinded to treatment group Number of centres: Multicentre, no other details Design: Parallel Power calculation: yes based on a previous trial Number of women randomised: 133 Number of women analysed: 125 fully completed the study Number of withdrawals and reasons: 8 lost to follow up Intention-to-treat analysis: no Source of funding: No details
Participants	Inclusion criteria: normoprolactinaemic, normogonadotropic, primary infertility with oligomenorrhoea or amenorrhoea, age 20-40 years, duration of primary infertility >2 years, no history of ovulation induction treatment and thyroid disease, normal results on hysterosalpingogram, husband with normal semen analysis according to WHO criteria Age: CC+hCG group 26.2±3.4 years; CC alone group 26.7±3.2 years Duration of infertility: CC+hCG group 2.91±2.0 years; CC alone group 2.88±2.0 years Source of women: Infertility units (May 2002 to April 2004) Exclusion criteria: no details Location: Turkey

Yilmaz 2006 (*Continued*)

Interventions	Day 1 was start of menses, clomiphene administered on days 5-9 Treatment(s): Clomiphene citrate 50mg + hCG (Pregnyl 10,000IU IM) when follicles reached 18mm in diameter as determined by ultrasound (n=60) Control or placebo: Clomiphene citrate 50 mg (n=65) Timed intercourse was advised 5 days after the last dose of clomiphene citrate for alternate days in both groups Duration: One cycle
Outcomes	Relevant outcomes: ovulation and pregnancy rates, clinical pregnancy rate, fertilisation rate, implantation rate, twin rate, abortion rate (detected chemically but not by ultrasound scan at 7 weeks), corpus luteum function, mid-luteal serum progesterone and luteal phase length
Notes	Pregnancy test (at 16th day after ovulation by serum ß-hCG), positive fetal heart rate at 7 weeks

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number tables
Allocation concealment?	Unclear	Opaque envelope technique
Blinding? All outcomes	Unclear	Sonographers evaluating follicle size were blinded to treatment group
Incomplete outcome data addressed? All outcomes	Unclear	133 randomised, 125 completed the trial fully and were analysed. 8 women lost to follow up; no details of adverse events, no report of live birth
Free of selective reporting?	No	No details of adverse events, no report of live birth

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Omari 2002	This was a conference abstract superseded by full paper (see Al-Omari 2004)
Al-Omari 2004	Study using letrozole, excluded in update 2009
Archer 1989	Participants not anovulatory

(*Continued*)

Armeanu 1992	Not a RCT
Atay 2006	Study using letrozole, excluded in update 2009
Aygen 2007	Study using letrozole, excluded in update 2009
Badawy 2008	Study compares with HmG which does not fit with selection criteria
Bayer 2006	Study using letrozole, excluded in update 2009
Connaughton 1974	Crossover trial, not all participants anovulatory, was included in Hughes 1996
Echt 1969	Population selection based on diagnosis of luteal phase defect
el Tabbakh 1988	Did not involve anti-oestrogen therapy
Elnashar 2006	This is a conference abstract of a paper published in full and included in the review
Gerhard 1979	Not a RCT
Glasier 1989	Participants not anovulatory
Greenblatt 1961	Not a RCT
Ito 1990	Not a RCT
Johnson 1990	Not oral agents
Koloszar 1996	Does not appear to be an RCT
Kubota 1992	Not a RCT
Lisse 1980	Not a RCT
Lobo 1982	Not a RCT
Mendes 1999	WHO group 1 women only
Mitwally 2001a	Not a RCT
Mitwally 2001b	Not a RCT
Presl 1984	Does not appear to be an RCT
Roozenburg 1997	Does not compare included interventions
Ruiz-Velasco 1978	Not a RCT

(*Continued*)

Senior 1978	6/9 participants not anovulatory
Singh 1992	Not a RCT
Trott 1996	Not a RCT
Tsuiki 1984	Not a RCT
Williamson 1973	Not a RCT

Characteristics of studies awaiting assessment *[ordered by study ID]*

Buvat 1987

Methods	Randomised trial
Participants	66 infertile women, infertile for at least one year n= 26 eugonadal anovulation, n=40 luteal phase inadequacy; no other severe infertility factor
Interventions	Clomiphene citrate 25-50mg/day versus tamoxifen 20mg/day
Outcomes	Pregnancy, multiple pregnancy, adverse events
Notes	Unable to separate anovulatory data from luteal phase deficiency data. Unable to contact author

Cabau 1990

Methods	Double-blind randomised trial, randomisation using permuted blocks of 10.Numbered boxes from laboratory with no distinguishing marks
Participants	300 women who had to be childless and referred for anovulatory cycles, irregular cycles with or without ovulation or dysovulatory cycles. Also included women with slight insufficiency of mucus and those with idiopathic sterility. Trying to get pregnant for at least one year or, had already received treatment for sterility, or had suffered a miscarriage and tried for at least 6 months to get pregnant again Excluded all women who physician did not want to prescribe placebo, >38 years old, amenorrhoea > 6 months duration, known tubal sterility,distinctly insufficient or infected mucus, partners presenting with deficiency in semen, women undergoing artificial insemination
Interventions	Cyclofenil 400mg taken on days 4-8 of menstrual cycle or day 5-8 n=114 versus placebo n=99
Outcomes	Live birth, miscarriage, foetal death
Notes	Unable to separate anovulatory data. Unable to contact authors

Senior 1978a

Methods	Randomised crossover trial
Participants	Nine infertile women (3 with anovulation and 6 with suspected luteal phase deficiency)
Interventions	Clomiphene for 2 months, tamoxifen for 2 months and placebo for one month before and one month between interventions
Outcomes	Ovulation and pregnancy,hormonal assays
Notes	Unable to extract anovulatory women from luteal deficiency data; unable to contact authors

DATA AND ANALYSES

Comparison 1. Anti-oestrogen versus no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clomiphene versus placebo	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pregnancy rate (per woman)	3	133	Odds Ratio (M-H, Fixed, 95% CI)	5.77 [1.55, 21.48]
1.2 Ovulation rate (per woman)	3	133	Odds Ratio (M-H, Fixed, 95% CI)	7.47 [3.24, 17.23]

Comparison 2. Anti-oestrogen versus anti-oestrogen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clomiphene versus tamoxifen	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pregnancy rate (per woman)	2	190	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.46, 1.94]
1.2 Ovulation rate (per woman)	1	95	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.66, 3.40]
1.3 Miscarriage rate (per woman)	1	86	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.01, 9.45]
1.4 Live birth rate (per woman)	1	95	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.25]
1.5 On-going pregnancy rate (per woman)	1	95	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.67]
2 Clomiphene plus tamoxifen versus clomiphene	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Pregnancy rate (per woman)	1	20	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.12, 91.60]
2.2 Ovulation rate (per woman)	1	20	Odds Ratio (M-H, Fixed, 95% CI)	14.54 [0.67, 316.69]

Comparison 3. Anti-oestrogen plus medical adjunct versus anti-oestrogen alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clomiphene plus ketoconazole versus clomiphene	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pregnancy rate (per woman)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	2.37 [0.88, 6.40]
1.2 Multiple pregnancy (per woman)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.37, 3.78]
1.3 Spontaneous abortion (after cord pulse)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 7.08]
2 Clomiphene plus bromocriptine versus clomiphene	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Pregnancy rate (per woman)	1	100	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.33, 2.96]
2.2 Ovulation rate (per woman)	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.47, 3.79]
3 Clomiphene plus dexamethasone versus clomiphene	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Pregnancy rate (per woman)	3	374	Odds Ratio (M-H, Fixed, 95% CI)	9.46 [5.05, 17.70]
3.2 Ovulation rate (per woman)	3	374	Odds Ratio (M-H, Fixed, 95% CI)	14.65 [8.76, 24.49]
3.3 Multiple pregnancy (per woman)	2	144	Odds Ratio (M-H, Fixed, 95% CI)	7.71 [0.38, 155.64]
4 Clomiphene plus combined oral contraceptive vs clomiphene	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Pregnancy rate (per woman)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	27.18 [3.14, 235.02]
4.2 Ovulation rate (per woman)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	26.71 [4.91, 145.38]
4.3 Miscarriage rate (per woman)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.97]
4.4 Multiple pregnancy (per woman)	1	48	Odds Ratio (M-H, Fixed, 95% CI)	7.98 [0.39, 163.33]
5 Clomiphene plus hCG versus clomiphene alone	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Ovulation rate (per woman)	2	192	Odds Ratio (M-H, Fixed, 95% CI)	3.48 [1.71, 7.06]
5.2 Pregnancy rate (per woman)	2	192	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.59, 2.36]
5.3 Clinical pregnancy rate (per woman)	1	125	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.61, 2.80]
5.4 Multiple pregnancies (per woman)	1	125	Odds Ratio (M-H, Fixed, 95% CI)	2.21 [0.19, 24.98]
5.5 Spontaneous abortion/miscarriage	2	192	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.19, 2.62]

6 Clomiphene versus clomiphene plus hormone supplementation	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Ovulation rate (per woman)	1	65	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.42, 4.27]
6.2 Pregnancy rate (per woman)	1	65	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.07, 2.48]
6.3 Adverse events	1	65	Odds Ratio (M-H, Fixed, 95% CI)	4.85 [0.22, 104.99]

Analysis 1.1. Comparison 1 Anti-oestrogen versus no treatment or placebo, Outcome 1 Clomiphene versus placebo.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 1 Anti-oestrogen versus no treatment or placebo

Outcome: 1 Clomiphene versus placebo

Study or subgroup	Placebo n/N	Clomiphene n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Pregnancy rate (per woman)					
Cudmore 1966	1/13	0/9		22.3 %	2.28 [0.08, 62.43]
Garcia 1985	8/24	2/22		59.5 %	5.00 [0.93, 26.91]
Johnson 1966	5/33	0/32		18.2 %	12.54 [0.66, 236.90]
Subtotal (95% CI)	**70**	**63**		**100.0 %**	**5.77 [1.55, 21.48]**
Total events: 14 (Placebo), 2 (Clomiphene)					
Heterogeneity: Chi^2 = 0.60, df = 2 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 2.61 (P = 0.0090)					
2 Ovulation rate (per woman)					
Cudmore 1966	8/13	2/9		21.3 %	5.60 [0.81, 38.51]
Garcia 1985	20/24	8/22		32.6 %	8.75 [2.20, 34.81]
Johnson 1966	17/33	4/32		46.1 %	7.44 [2.13, 25.97]
Subtotal (95% CI)	**70**	**63**		**100.0 %**	**7.47 [3.24, 17.23]**
Total events: 45 (Placebo), 14 (Clomiphene)					
Heterogeneity: Chi^2 = 0.14, df = 2 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 4.72 (P < 0.00001)					

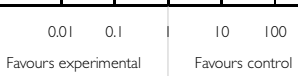
Analysis 2.1. Comparison 2 Anti-oestrogen versus anti-oestrogen, Outcome 1 Clomiphene versus tamoxifen.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 2 Anti-oestrogen versus anti-oestrogen

Outcome: 1 Clomiphene versus tamoxifen

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Pregnancy rate (per woman)					
Boonstanfar 2001	6/47	10/48		57.4 %	0.56 [0.18, 1.68]
Vegetti 1999	12/50	8/45		42.6 %	1.46 [0.54, 3.98]
Subtotal (95% CI)	**97**	**93**		**100.0 %**	**0.94 [0.46, 1.94]**
Total events: 18 (Experimental), 18 (Control)					
Heterogeneity: Chi^2 = 1.61, df = 1 (P = 0.20); I^2 =38%					
Test for overall effect: Z = 0.16 (P = 0.87)					
2 Ovulation rate (per woman)					
Boonstanfar 2001	30/47	26/48		100.0 %	1.49 [0.66, 3.40]
Subtotal (95% CI)	**47**	**48**		**100.0 %**	**1.49 [0.66, 3.40]**
Total events: 30 (Experimental), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.34)					
3 Miscarriage rate (per woman)					
Boonstanfar 2001	0/40	1/46		100.0 %	0.37 [0.01, 9.45]
Subtotal (95% CI)	**40**	**46**		**100.0 %**	**0.37 [0.01, 9.45]**
Total events: 0 (Experimental), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
4 Live birth rate (per woman)					
Boonstanfar 2001	1/47	3/48		100.0 %	0.33 [0.03, 3.25]
Subtotal (95% CI)	**47**	**48**		**100.0 %**	**0.33 [0.03, 3.25]**
Total events: 1 (Experimental), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
5 On-going pregnancy rate (per woman)					
Boonstanfar 2001	1/47	5/48		100.0 %	0.19 [0.02, 1.67]
Subtotal (95% CI)	**47**	**48**		**100.0 %**	**0.19 [0.02, 1.67]**
Total events: 1 (Experimental), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.50 (P = 0.13)					

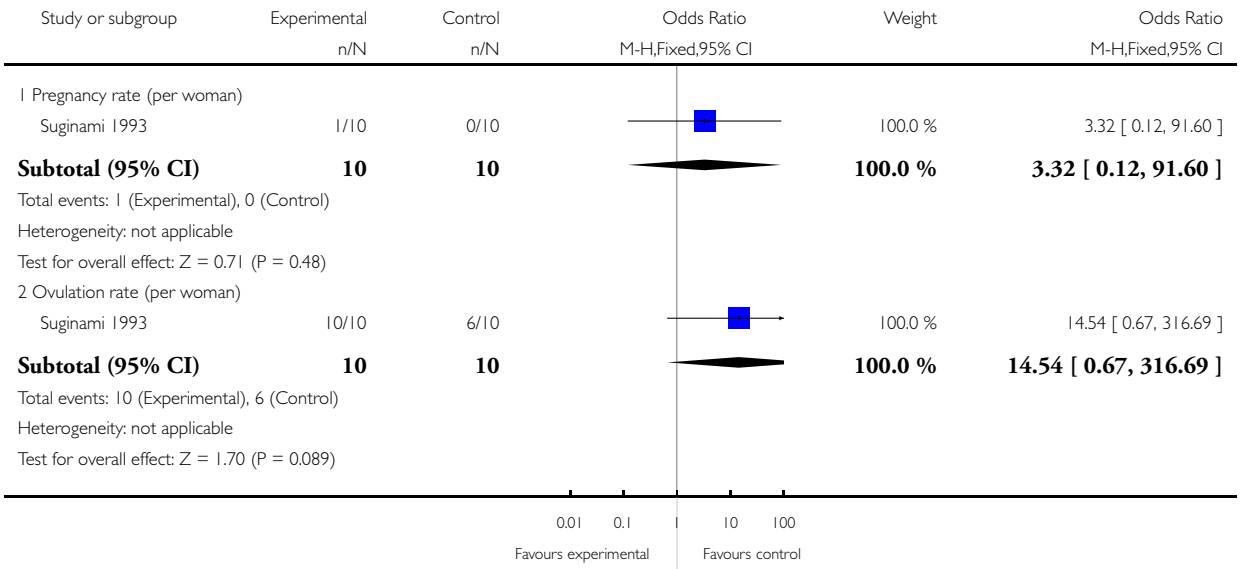


Analysis 2.2. Comparison 2 Anti-oestrogen versus anti-oestrogen, Outcome 2 Clomiphene plus tamoxifen versus clomiphene.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 2 Anti-oestrogen versus anti-oestrogen

Outcome: 2 Clomiphene plus tamoxifen versus clomiphene

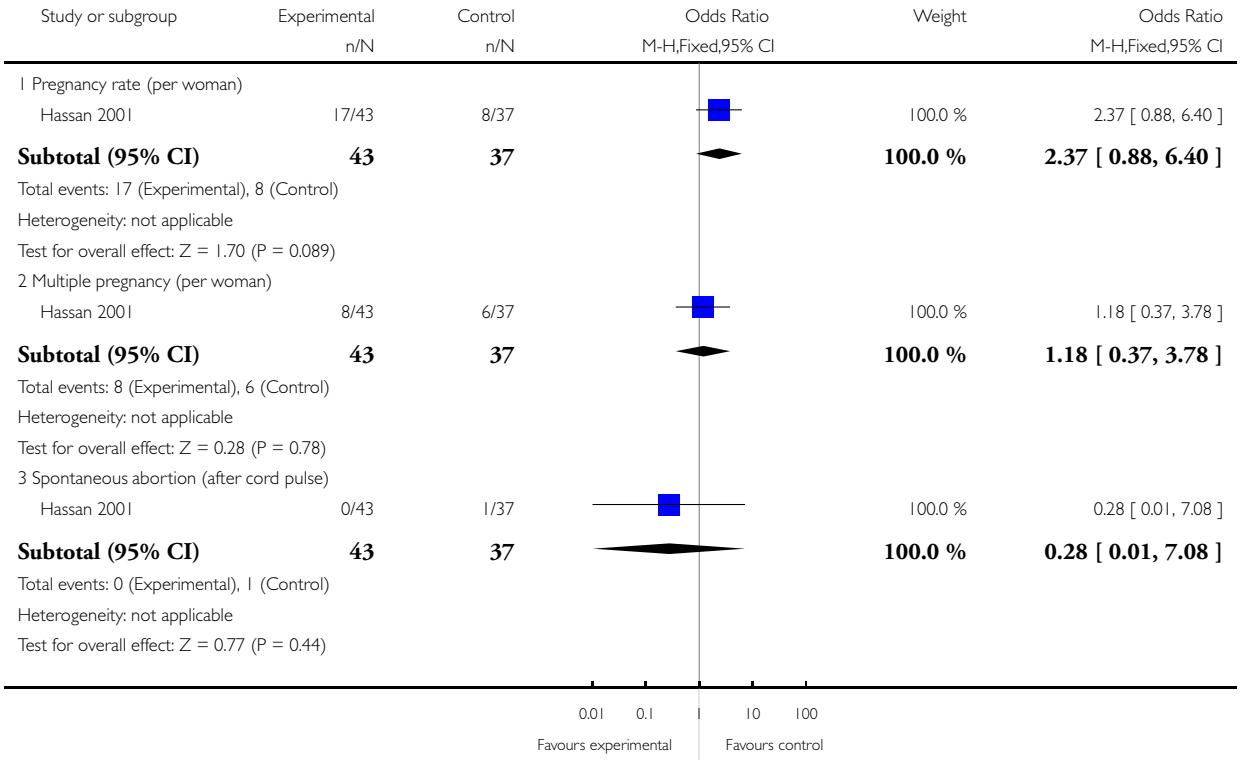


Analysis 3.1. Comparison 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, Outcome 1 Clomiphene plus ketoconazole versus clomiphene.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone

Outcome: 1 Clomiphene plus ketoconazole versus clomiphene

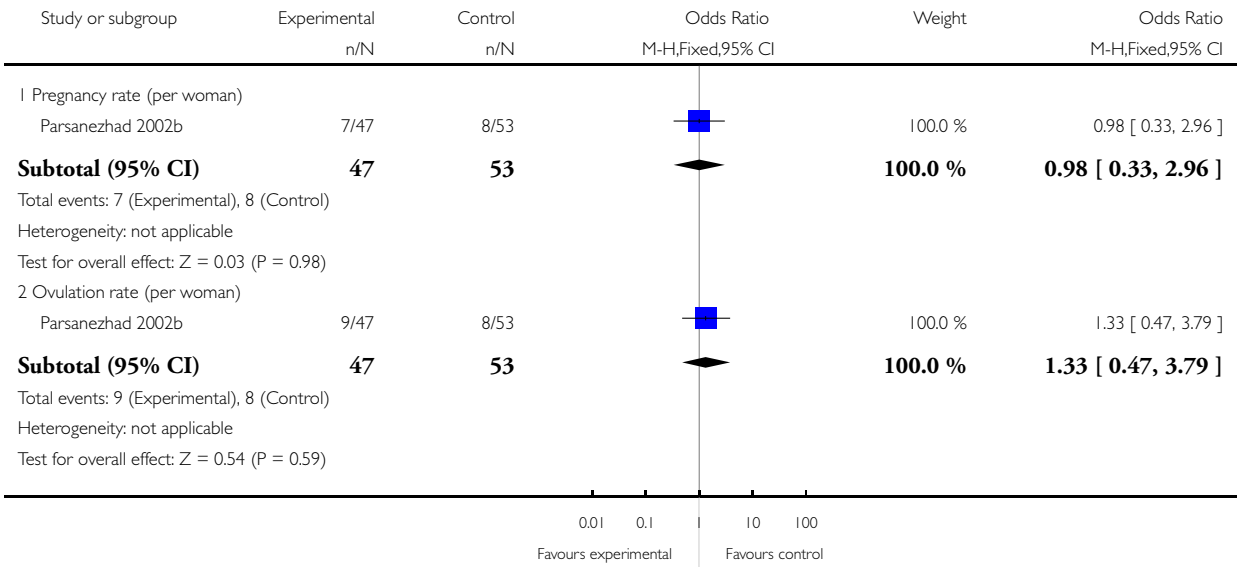


Analysis 3.2. Comparison 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, Outcome 2 Clomiphene plus bromocriptine versus clomiphene.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone

Outcome: 2 Clomiphene plus bromocriptine versus clomiphene

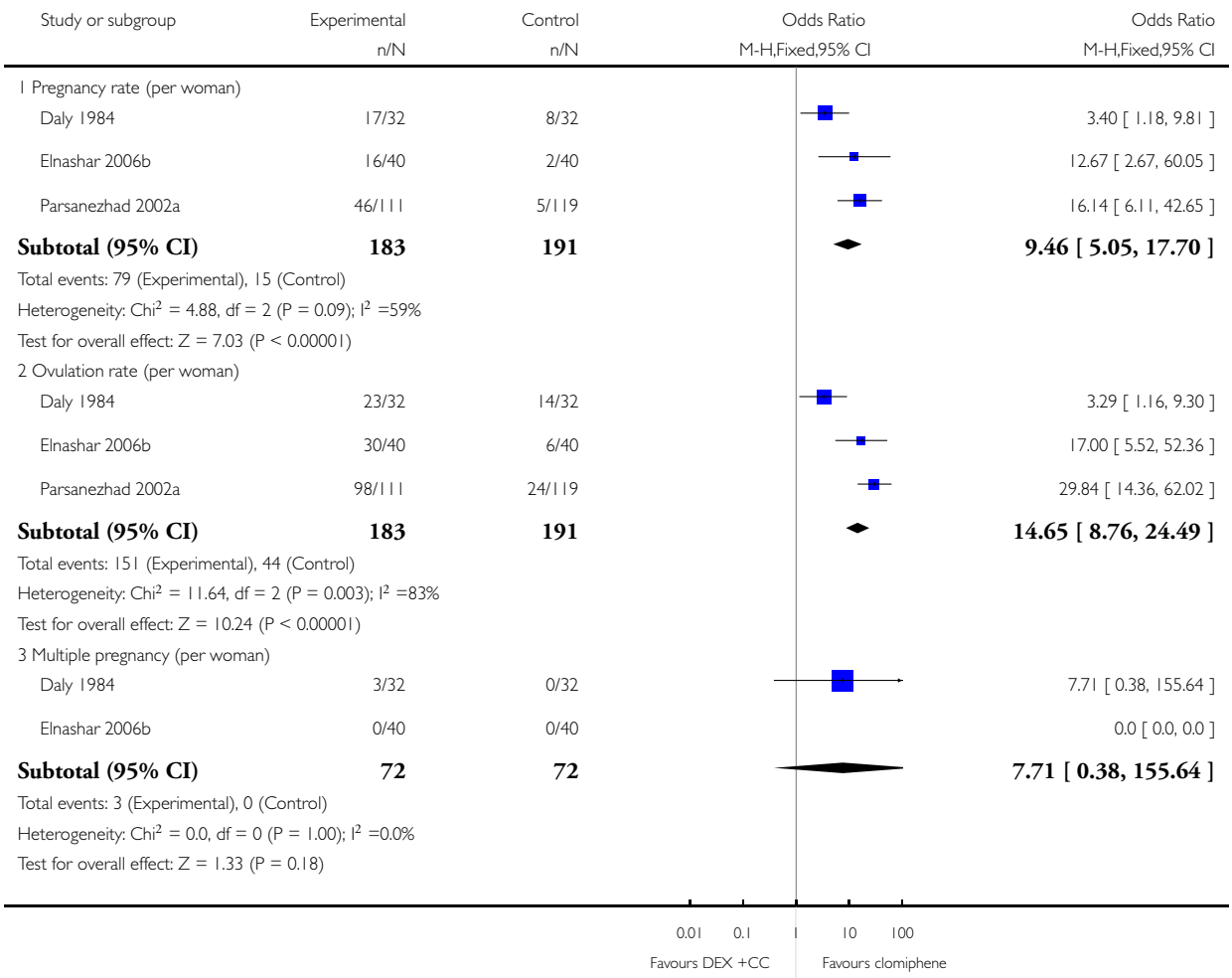


Analysis 3.3. Comparison 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, Outcome 3 Clomiphene plus dexamethasone versus clomiphene.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone

Outcome: 3 Clomiphene plus dexamethasone versus clomiphene

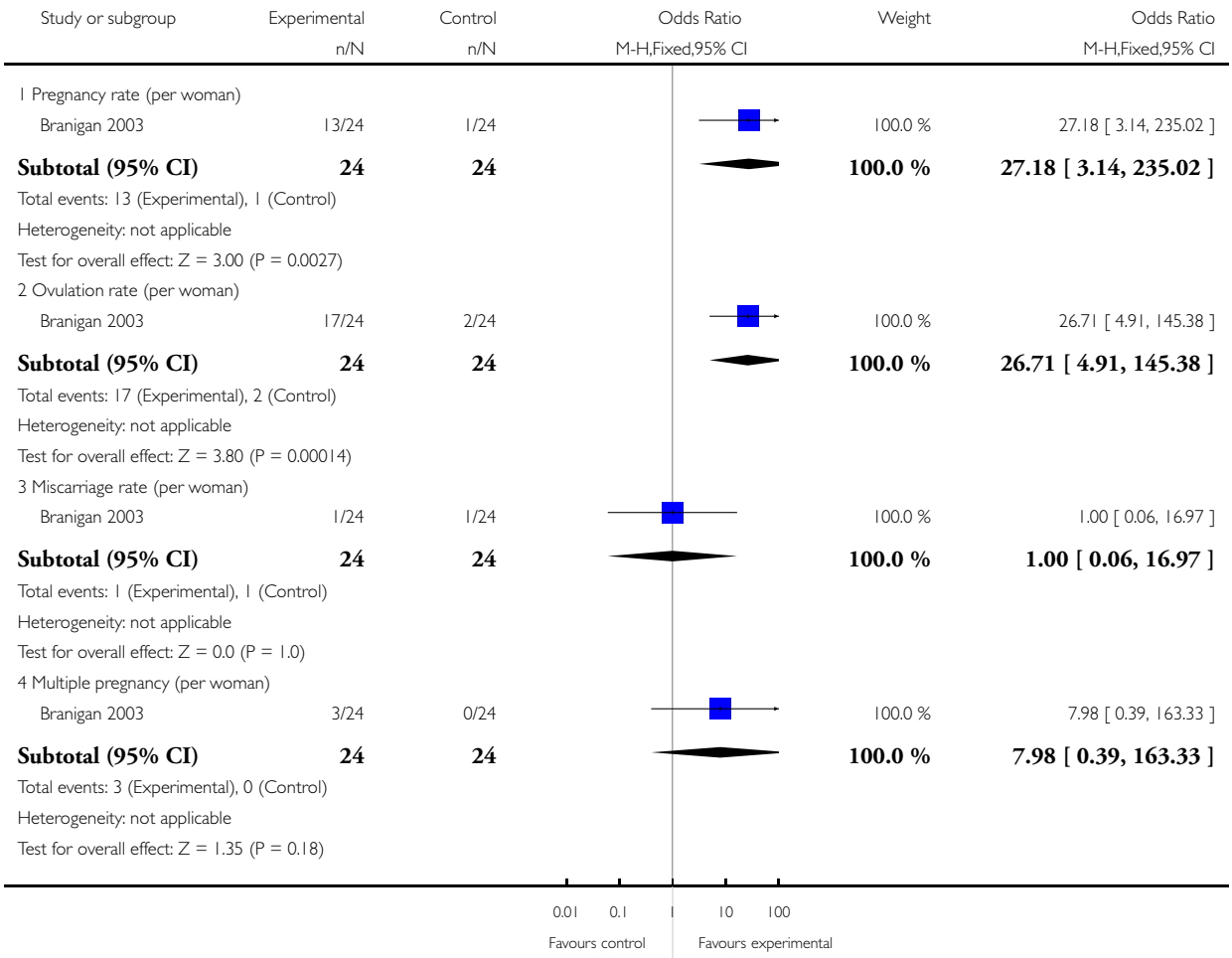


Analysis 3.4. Comparison 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, Outcome 4 Clomiphene plus combined oral contraceptive vs clomiphene.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone

Outcome: 4 Clomiphene plus combined oral contraceptive vs clomiphene

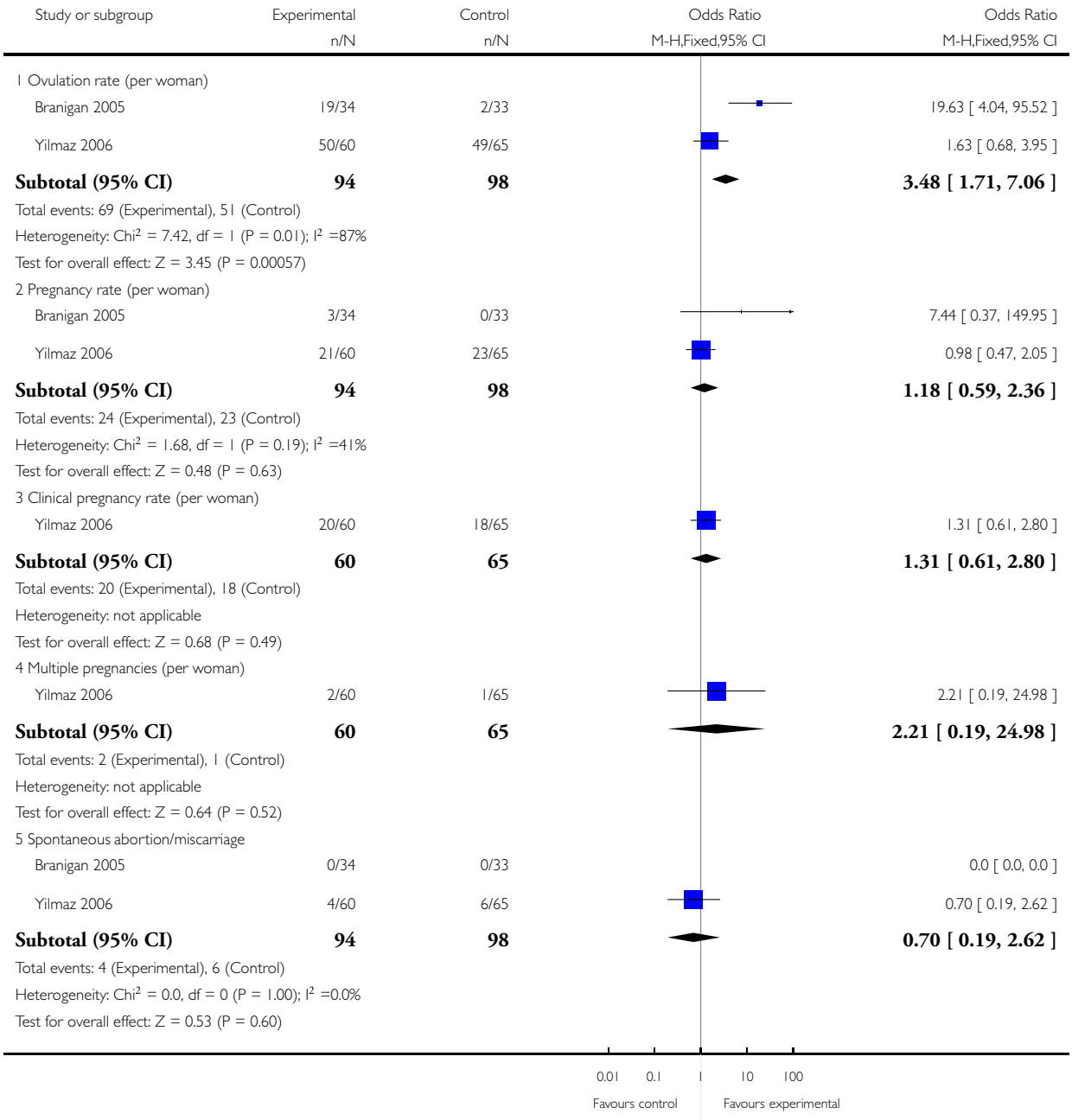


Analysis 3.5. Comparison 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, Outcome 5 Clomiphene plus hCG versus clomiphene alone.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone

Outcome: 5 Clomiphene plus hCG versus clomiphene alone

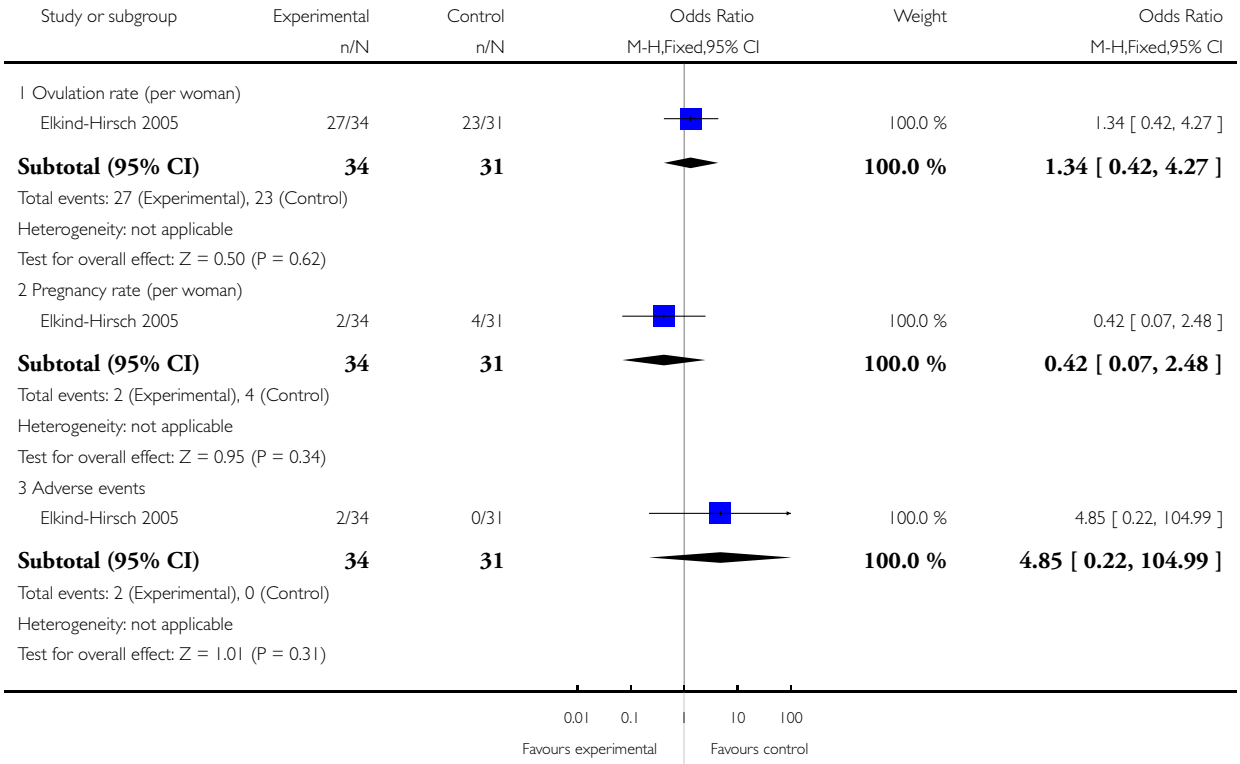


Analysis 3.6. Comparison 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, Outcome 6 Clomiphene versus clomiphene plus hormone supplementation.

Review: Clomiphene and anti-oestrogens for ovulation induction in PCOS

Comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone

Outcome: 6 Clomiphene versus clomiphene plus hormone supplementation



APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) <1950 to April Week 3 2009>
Search Strategy:

---

1 exp Polycystic Ovary Syndrome/ or PCOS.mp. (7568)
2 polycystic ovar$.mp. (8536)
3 PCOD.mp. (250)
4 (stein-leventhal or leventhal).tw. (641)
5 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (52)
6 Anovulation/ (1736)

7 anovulat$.ti,ab,sh. (4380)
8 oligo ovulat$.tw. (56)
9 PCO.tw. (2509)
10 or/1-9 (13868)
11 infertility/ or infertility, female/ (26518)
12 infertil$.ti,ab,sh. (52554)
13 steril$.tw. (49945)
14 subfertil$.tw. (2444)
15 or/11-14 (96743)
16 10 and 15 (2855)
17 randomized controlled trial.pt. (268708)
18 controlled clinical trial.pt. (78997)
19 randomized controlled trials as topic/ (59658)
20 random allocation/ (63854)
21 double blind method/ (100749)
22 single blind method/ (12769)
23 or/17-22 (453925)
24 animals/ not (animals/ and humans/) (3268483)
25 23 not 24 (423575)
26 clinical trial.pt. (451033)
27 exp clinical trials as topic/ (211898)
28 (clinic$ adj25 trial$).ti,ab. (157040)
29 cross-over studies/ (23742)
30 (crossover or cross-over or cross over).tw. (42520)
31 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (100643)
32 placebos/ (27791)
33 placebo$.ti,ab. (115318)
34 random$.ti,ab. (438025)
35 research design/ (55533)
36 or/26-35 (971010)
37 36 not 24 (898829)
38 25 or 37 (925219)
39 16 and 38 (427)
40 (2008$ or 2009$).ed. (964151)
41 39 and 40 (51)
42 from 41 keep 1-51 (51)

Appendix 2. Embase search strategy

Database: EMBASE <1980 to 2009 Week 17>
Search Strategy:
---
1 exp ovary polycystic disease/ or exp stein leventhal syndrome/ or exp ovary insufficiency/ or exp anovulation/ (12370)
2 (polycystic adj5 ovar$).tw. (6461)
3 (PCOS or PCOD).tw. (3549)
4 stein leventhal.tw. (69)
5 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (31)
6 anovulat$.tw. (2818)
7 oligo ovulat$.tw. (39)
8 PCO.tw. (1614)
9 (ovar$ adj5 insufficien$).tw. (228)
10 or/1-9 (14952)

11 exp infertility/ or exp female infertility/ or exp subfertility/ (45099)
12 (infertil$ or subfertil$ or steril$).tw. (58314)
13 or/11-12 (80103)
14 10 and 13 (7394)
15 Controlled study/ or randomized controlled trial/ (2889905)
16 double blind procedure/ (72216)
17 single blind procedure/ (8128)
18 crossover procedure/ (21239)
19 drug comparison/ (81258)
20 placebo/ (126023)
21 random$.ti,ab,hw,tn,mf. (436937)
22 latin square.ti,ab,hw,tn,mf. (1128)
23 crossover.ti,ab,hw,tn,mf. (36525)
24 cross-over.ti,ab,hw,tn,mf. (12284)
25 placebo$.ti,ab,hw,tn,mf. (177308)
26 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf. (118594)
27 (comparative adj5 trial$).ti,ab,hw,tn,mf. (15942)
28 (clinical adj5 trial$).ti,ab,hw,tn,mf. (606766)
29 or/15-28 (3424433)
30 nonhuman/ (3214641)
31 animal/ not (human/ and animal/) (14485)
32 or/30-31 (3218339)
33 29 not 32 (2022942)
34 14 and 33 (2269)
35 limit 34 to yr="2006 - 2008" (667)
36 (hyperprolactinaem$ or cushing$).tw. (7315)
37 35 not 36 (661)
38 chemotherap$.tw. (167085)
39 37 not 38 (620)
40 cancer.tw. (553793)
41 39 not 40 (583)
42 (200806$ or 200807$ or 200808$ or 200809$ or 200810$ or 200811$ or 200812$).em. (87205)
43 2009$.em. (186762)
44 43 or 42 (273967)
45 44 and 41 (49)
46 from 45 keep 1-49 (49)

Appendix 3. psychINFO search strategy

1 exp Polycystic Ovary Syndrome/ or PCOS.mp. (65)
2 polycystic ovar$.mp. (125)
3 PCOD.mp. (5)
4 (stein-leventhal or leventhal).tw. (194)
5 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (0)
6 Anovulation/ (0)
7 anovulat$.ti,ab,sh. (88)
8 oligo ovulat$.tw. (0)
9 PCO.tw. (144)
10 or/1-9 (546)
11 infertility/ or infertility, female/ (1175)
12 infertil$.ti,ab,sh. (1741)
13 steril$.tw. (1924)

14 subfertil$.tw. (36)
15 or/11-14 (3616)
16 10 and 15 (22)
17 limit 16 to yr="2008 -Current" (2)
18 from 17 keep 1-2 (2)

Appendix 4. CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2009>
Search Strategy:
---
1 exp Polycystic Ovary Syndrome/ or PCOS.mp. (570)
2 polycystic ovar$.mp. (718)
3 PCOD.mp. (21)
4 (stein-leventhal or leventhal).tw. (5)
5 (ovar$ adj (scelerocystic or polycystic or degeneration)).tw. (1)
6 Anovulation/ (78)
7 anovulat$.ti,ab,sh. (250)
8 oligo ovulat$.tw. (9)
9 PCO.tw. (209)
10 or/1-9 (1112)
11 infertility/ or infertility, female/ (832)
12 infertil$.ti,ab,sh. (1864)
13 steril$.tw. (1594)
14 subfertil$.tw. (113)
15 or/11-14 (3460)
16 10 and 15 (225)
17 limit 16 to yr="2008 -Current" (11)
18 from 17 keep 1-11 (11)

WHAT'S NEW

Last assessed as up-to-date: 21 June 2009.

Date	Event	Description
23 June 2009	New search has been performed	Nine new studies identified, review updated.
16 June 2009	New citation required but conclusions have not changed	In June 2009 the title was changed to Clomiphene and anti-oestrogens for ovulation induction in PCOS and new search completed. Nine additional studies identified in update

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 1, 2005

Date	Event	Description
16 June 2009	Amended	Aromatse inhibitors removed from text as part of separate review
19 February 2009	Amended	changes made to structure of text and presentation of findings
9 June 2008	Amended	Converted to new review format.
7 November 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Julie Brown: wrote the updated version of this review including identification of new trials, data extraction and analysis.

Cindy Farquhar: initiated and conceptualised the protocol, commented on drafts of the original and updated review and assisted in the identification of new trials and data extraction for the review update.

Clare Boothroyd: wrote the initial version of the protocol and commented on drafts of the review.

James Beck: updated the protocol and performed the primary literature search, initial assessment of trials and quality analysis, data collection, analysis and wrote the initial draft of the review.

Michelle Proctor: checked the literature search, reviewed quality analysis and data collection, checked and revised the initial draft of the review.

Edward Hughes: provided clinical input for the review and commented on drafts of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Newcastle Upon Tyne, School of Medicine, Newcastle Upon Tyne, UK.
- University of Auckland, School of Medicine, Auckland, New Zealand.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The inclusion criteria of this review were widened from that of the original protocol (participants with anovulation attributed to PCOS) to include all WHO group 2 causes of anovulation but excluding hyperprolactinaemia. Trials that were non-specific but appeared to describe PCOS-like anovulation (for example participants with progestin-induced withdrawal bleeding) were included. Due to the age of many of the trials, particularly for clomiphene versus placebo, the most likely cause of anovulation was not described fully. In particular, the currently utilised diagnostic criteria for PCOS were not able to be met. These trials would have been excluded under the criteria of the protocol. It was felt that their results were valid and important and so the background and inclusion criteria sections were widened.

Aromatase inhibitor comparisons have been removed from this review as they will addressed within a separate protocol El Daly 2006.

Title changed from 'Oral anti-oestrogens and medical adjuncts for subfertility associated with anovulation' to 'Clomiphene and anti-oestrogens for ovulation induction in PCOS.

INDEX TERMS

Medical Subject Headings (MeSH)

Anovulation [*complications; drug therapy]; Clomiphene [therapeutic use]; Contraceptives, Oral, Combined [therapeutic use]; Dexamethasone [therapeutic use]; Drug Therapy, Combination [methods]; Estrogen Antagonists [*therapeutic use]; Infertility, Female [*drug therapy; etiology]; Polycystic Ovary Syndrome [complications]; Randomized Controlled Trials as Topic; Tamoxifen [therapeutic use]

MeSH check words

Female; Humans