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Oral versus injectable ovulation induction agents for unexplained subfertility (Review)

Athaullah N, Proctor M, Johnson N

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[Intervention Review]

Oral versus injectable ovulation induction agents for unexplained subfertility

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ABSTRACT

Background

Oral (anti-oestrogens) and injectable (gonadotrophins) ovulation induction agents have been used to increase the number of eggs produced by a woman per cycle in treatment for unexplained subfertility. It is unclear whether there are significant advantages of one type of treatment over the other in this context or in terms of fertility.

Objectives

To assess the efficacy of oral versus injectable ovulation induction agents for unexplained subfertility.

Search methods

The search strategy of the Menstrual Disorders and Subfertility Group was used for the identification of relevant randomised controlled trials.

Selection criteria

All trials where oral ovulation induction agents were compared with injectable ovulation induction agents in treatment groups generated by randomisation, from couples with unexplained subfertility, were considered for inclusion in the review.

Data collection and analysis

Five randomised controlled trials, including a total of 231 identified couples with unexplained subfertility, were found and included in this review. All trials were assessed for quality criteria. The studied outcomes were pregnancy, live birth, miscarriage, multiple birth, occurrence of ovarian hyperstimulation syndrome and cycle cancellation.

Main results

Where trials with important co-interventions were excluded, there was no significant difference in the odds of beneficial outcomes for oral versus injectable ovulation induction agents - live birth per couple (OR 0.06, 95%CI 0.00 to 1.15), pregnancy per woman (OR 0.33, 95%CI 0.09 to 1.20); nor of detrimental outcomes for injectable versus oral agents - miscarriage (OR 0.11, 95%CI 0.00 to 2.84); there were no reported cases of multiple births, cases of ovarian hyperstimulation or discontinued cycles consequent upon overstimulation.

Where trials with the co-intervention of a human chorionic gonadotrophin trigger injection (given only in the injectable ovulation induction agent treatment arm) were not excluded there was no significant difference in the odds of live birth per couple (OR 0.40, 95%CI 0.15 to1.08). However oral ovulation induction agents had significantly reduced odds of pregnancy per woman compared to injectable ovulation induction agents (OR 0.41, 95%CI 0.17 to 0.80). For detrimental outcomes, there were no significant differences in the odds of miscarriage (OR 0.61, 95%CI 0.09 to 4.01) and multiple birth (OR 1.08, 95%CI 0.16 to 7.03) for injectable versus oral agents. No data were available concerning the occurrence of ovarian hyperstimulation syndrome nor cycle cancellation.

Authors' conclusions

There is insufficient evidence to suggest that oral agents are inferior or superior to injectable agents in the treatment of unexplained subfertility. Information on harms is sketchy, and remains compatible with large differences in either direction. Much larger trials than have previously been undertaken are required to provide information on relative harms as well as benefits.

PLAIN LANGUAGE SUMMARY

Oral versus injectable ovulation induction agents for unexplained subfertility

For many couples who cannot become pregnant, no reason is apparent after investigation (unexplained infertility). One treatment option for these couples is for the woman to be given medications to increase the number of eggs she produces each cycle. This treatment is also sometimes combined with a technique of purifying the partner's sperm and injecting it through the woman's cervix at her fertile time. This review of trials looked at which type of these medications, oral-form or injection-form, were the best in producing the most successful outcome. The review found no significant benefit of using one type of medication (oral or injectable) over the other, although there were insufficient data from trials. More research is needed to examine this question.

BACKGROUND

The management of subfertility in couples has many different avenues for investigation and treatment, dependent upon the cause of the subfertility. This review deals with couples whose subfertility is unexplained.

Unexplained subfertility is a diagnosis of exclusion, when the standard investigation of both the female and male partner has ruled out other causes of subfertility. In short, the diagnosis encompasses women who can ovulate plus have patent fallopian tubes and there is no male factor subfertility. It does not mean that there is no reason for the subfertility, but that the reason is unable to be identified by routine investigation at that time. Approximately 10 to 15 percent of infertile couples will receive the diagnosis of unexplained subfertility.

Ovulation induction is a rational treatment for women who fail to ovulate. The theory is to encourage the ovaries to produce oocytes (eggs from an ovary), in the hope that they will be available for fertilisation by the male's sperm leading to pregnancy. This theory is extended for treating unexplained subfertility, where the intention is to induce multiple follicular development, where more than one egg is produced - thus increasing the likelihood of fertilisation. Treatments commonly used to induce ovulation are broadly divided into two categories with respect to how they are given to the woman, oral and injectable.

Oral treatments, such as clomiphene citrate or tamoxifen are anti-oestrogens which release the hypothalamus and pituitary gland from the negative feedback effects of oestrogen. The release of gonadotrophin releasing-hormone (GnRH) is enhanced. This hormone stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. FSH and LH promote follicle development in the ovary and ovulation respectively. This method is often referred to as the indirect way of increasing gonadotrophins, as opposed to the more direct approach of injectable treatments.

The injectable treatments are gonadotrophins designed to have an action similar to FSH, exerting an effect directly on the ovary to promote follicular development. The first preparations of FSH were extracted from cadaver (a dead person) pituitary glands. However, this was an expensive process and raised concerns about the risk of transmission of Creutzfeldt-Jakob Disease (CJD) - as CJD is believed to cross species via brain, spinal cord and other nervous tissue. These preparations were replaced by urinary gonadotrophins such as human menopausal gonadotrophins (hMG),

which have significant LH activity in addition to FSH activity. Another drug, urofollitrophin, is a urinary gonadotrophin of higher purity with less LH activity, often referred to as high purity urinary gonadotrophin. The most recent development is the use of genetic based technology to produce recombinant FSH (r-FSH), the purest exogenous form of this hormone.

Ovulation induction agents have an established role in the treatment of subfertility in women who cannot ovulate (anovulation), in the case of clomiphene (Hughes (A) 2000), and in the case of gonadotrophins where the woman is resistant to clomiphene (Hughes (B) 2000). However the role of ovulation induction agents for controlled ovarian stimulation in unexplained subfertility is less clear. Although their is some evidence that their use might correct subtle cycle disorders such as luteal insufficiency (Murray 1989). The use of clomiphene compared to placebo or no treatment in unexplained subfertility has been shown to have a significant but small positive effect on the conception rate for couples with unexplained subfertility (Hughes (C) 2000), but this may be counterbalanced by the side effects with clomiphene including multiple pregnancy and symptoms including transient hot flushes and visual disturbances plus hyperstimulation. There has also been a reluctance amongst clinicians to prescribe clomiphene for more than six ovulatory cycles, because of suggestions that this long term use can lead to ovarian cancer (Balasch 1999).

However, does gonadotrophin therapy offer benefit over anti-oestrogens such as clomiphene in couples with unexplained subfertility? There maybe an increased likelihood of cancellation of a cycle due to over stimulation with gonadotrophin therapy. Ovarian hyperstimulation syndrome may also be a risk. The risk of multiple pregnancy and miscarriage must also be considered and finally there are increased costs associated with gonadotrophin therapy compared to oral ovulation agents. Therefore the use of gonadotrophin therapy for unexplained subfertility must be justifiable on the grounds of robust evidence of its effectiveness when compared with anti-oestrogens before it becomes standard clinical practice.

This review aims to summarise the evidence for gonadotrophin therapy versus anti-oestrogens for controlled ovarian stimulation in unexplained subfertility.

OBJECTIVES

The primary objective of this review was to compare the effectiveness of oral ovulation induction agents (anti-oestrogens) and injectable ovulation induction (gonadotrophins) treatments for controlled ovarian stimulation in the treatment of unexplained subfertility, in order to see which was of greater benefit. Benefit was assessed primarily as treatment leading to pregnancy and successful delivery. Secondary objectives of the review were to assess other outcomes, such as miscarriage, multiple birth, ovarian hyperstimulation syndrome and cycle cancellation. Though important, cost analyses were not performed in this review

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were used in the first instance, but non-randomised studies would have been considered in the absence of good quality RCTs.

Types of participants

Women receiving an ovulation induction agent where the couple has unexplained subfertility. The trialist's definition of unexplained subfertility was accepted provided they mentioned assessment for:

i) No evidence for tubal disease, demonstrated by a diagnostic tubal patency test.

ii) Normal ovulatory function demonstrated by biphasic body temperature chart, cervical mucus changes, LH testing of urine or serum and luteal phase serum progesterone level.

iii) Normal semen analysis, as described by the World Health Organisation (WHO).

Secondly women receiving an ovulation induction agent for a donor insemination cycle where the couple has male factor subfertility (since it is the intervention oral versus injectable ovulation induction agents, in the context of exposure to normal sperm, which is under scrutiny).

Types of interventions

Anti-oestrogens versus gonadotrophin therapy in the context of multiple follicular development for intercourse (whether timed or otherwise), or intrauterine insemination (IUI). It was planned to pool insemination techniques as long as no statistical heterogeneity was found. The following comparisons were considered:

1) anti-oestrogens versus pituitary-extract gonadotrophins

2) anti-oestrogens versus urinary gonadotrophins such as human menopausal gonadotrophin (hMG)

3) anti-oestrogens versus high purity urinary gonadotrophins

3) anti-oestrogens versus recombinant FSH (r-FSH)

4) anti-oestrogens alone versus "combination of anti-oestrogens and gonadotrophins"

5) gonadotrophins alone versus "combination of anti-oestrogens and gonadotrophins"

All dosages of interventions were considered. Trials assessing these interventions versus placebo or no treatment were not included,

as they are included in pre-existing meta-analyses (Hughes 1997 (meta); Hughes (C) 2000).

Types of outcome measures

Primary outcomes

1) Live birth rate (per woman or per cycle)

Secondary outcomes

2) Pregnancy rate per women - number of clinical pregnancies divided by the number of couples
3) Pregnancy rate per cycle - number of clinical pregnancies divided by the number of treatment cycles (data per couple are required for meaningful comparison, however pregnancy per cycle is reported more often in subfertility research. Reported numbers are given for information in the graphs, but it should be noted that the apparent confidence intervals are incorrect and that pooling the reported figures would be inappropriate.)
Pregnancy was defined by:
-fetal heart activity on ultrasound assessment
-trophoblastic tissue on pathologic exam at time of miscarriage or surgery for ectopic pregnancy
-positive urine or serum beta hCG (fetal heartbeat is preferable however and positive hCG is only a surrogate measure of pregnancy).
4) Miscarriage rate (as a ratio of total pregnancies).
5) Multiple birth rate (as a ratio of total pregnancies)
6) Ovarian hyperstimulation syndrome
7) Cycle cancellation as a result of over stimulation (as defined by the trialist; reported as the number of women with one or more cancelled cycles)

Search methods for identification of studies

All reports which described (or might have described) randomised controlled trials of anti-oestrogens versus gonadotrophin therapy for the treatment of unexplained subfertility were obtained using the following search strategy.
1) The Menstrual Disorders & Subfertility Group's Specialised Register of controlled trials was searched for any trials. See the Review Group for more details on the make-up of the Specialised Register.
2) The following electronic databases were searched using Ovid software;
Medline - 1966 to 2000
Embase - 1980 to 2000
Bio extracts - 1980 to 2000
The Medline, Embase and Bioabstract databases were searched using subject headings and keywords see Appendix 1
3) The Cochrane Controlled Trials Register (CCTR) on the Cochrane Library Issue 2, 2000 was also searched in all fields using the following words:
1. Clomiphene
2. Tamoxifen
3. GnRH or gonadotrophin
4. 1 and 2 and 3
4) The National Research Register (NRR), a register of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service, as well as entries from the Medical Research Council's Clinical Trials Register, and details on reviews in progress collected by the NHS Centre for Reviews and Dissemination, was searched for any trials with the following keywords,
1 clomiphene or clomid or serophene
2 tamoxifen or nolvadex
3 1 or 2
4 gonadotrophin or menotrophin or menotropin
5 hMG or FSH
6 gonal-f or puregon or follitropin or pergonal
7 humegon or menogon or normegon or metrodin or orgafol
8 4 or 5 or 6 or 7
The Clinical Trials register, a registry of federally and privately funded US clinical trials was also searched for the same keywords.
5) The citation lists of relevant publications, review articles, and included studies was also searched.

Data collection and analysis

Statistical analysis was performed in accordance with the statistical guidelines developed by the Cochrane Menstrual Disorders and Subfertility Group. The heterogeneity of the studies was analysed by inspecting the scatter in the data points and the overlap in the confidence intervals and more formally by checking the results of the chi-squared test. Apparent statistical heterogeneity was investigated informally by consideration of factors such as study quality. Where possible results of trials will be pooled. However in the case of statistical heterogeneity then trials with different insemination techniques will be considered separately.
For dichotomous data, two by two tables were generated for each trial and expressed as an odds ratio (OR) with 95% confidence intervals (CI). This data was combined for meta-analysis with RevMan software -using the Peto-modified Mantel-Haenszel method and a fixed effects model. It was expected that the majority of data would be dichotomous. Any continuous data would have been combined for meta-analysis with RevMan software using the weighted mean difference (WMD) with 95% CI and a fixed effects model.
In the graphical display of the meta-analyses, a benefit from oral ovulation induction agents (anti estrogens) would be displayed graphically to the right of the centre-line and a benefit from injectable ovulation induction agents (gonadotrophins) would be

displayed graphically to the left of the centre-line. Considering injectable agents, for an outcome such as pregnancy, an increase in odds is considered a benefit of intervention and thus such increased odds would be displayed to the left of the centre-line. For an outcome such as miscarriage, an increase in the odds is considered a detrimental effect of the intervention and thus such increased odds would be displayed to the right of the centre-line. This should be noted when the summary graphs are viewed for the assessment of the relative beneficial and detrimental effects of each intervention.

Whenever there were missing elements in the data, attempts were made to contact the investigators. If this was impossible, the reviewers have stated any assumptions that are used in the extraction and analysis of the data. Where there were cross-over trials, the reviewers used the first part of the trial, before cross over, as per Cochrane protocol

Separate sub-group meta-analyses, if there were a large enough number of trials included in the review, would be performed for trials comparing anti-oestrogens to different types of gonadotrophins, trials where donor insemination was used, and trials where a potentially influential co-intervention was used.

It was planned to undertake sensitivity analyses if there were more than ten trials included in the review to examine the stability of the results in relation to:

1) differences in methodological quality (inclusion of all trials compared to trials of high quality only);

2) trials using r-FSH studies compared with trials where other gonadotrophins were used;

3) trials using the partner's sperm in unexplained subfertility compared to trials using donor sperm in male factor subfertility;

4) inclusion of only trials with no co-intervention compared to inclusion of all trials.

However this was not performed because only six trials were included.

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

Selection of studies

The selection of studies for inclusion in the review was undertaken by two reviewers (Nat Athaullah and Michelle Proctor). The titles and abstracts of articles found in search were screened by Nat Athaullah, who discarded studies that were clearly ineligible but was overly inclusive rather than risk losing relevant studies. Both reviewers independently assessed whether the studies met the inclusion criteria, with disagreements resolved by a third reviewer (Neil Johnson), although none arose. Further information was sought from the authors where papers contained insufficient information to make a decision about eligibility

Data extraction and management

Nat Athaullah and Michelle Proctor independently extracted information using pro-forma's adapted from those designed by the Review Group. Discrepancies were resolved by discussion. For each included trial, information was collected regarding the following quality criteria and methodological details. Where possible, missing data was sought from the authors.

Trial Characteristics

1. Method of randomisation.
2. Presence or absence of blinding to treatment allocation.
3. Number of participants randomised, excluded, or lost to follow-up.
4. Whether an "intention to treat" analysis was done.
5. The presence of a power calculation.
6. Duration, timing and location of the study.
7. Study design: parallel or crossover
8. Sources of any funding.

Characteristics of the Study Participants

1. Definition and duration of pre-existing subfertility in both male and female
2. Method of assessment of unexplained subfertility (diagnostic techniques)
3. Previous administered treatment(s)
4. Age of participants, both male and female

Interventions Used

1. Type of treatment used.
2. Methodology of technique used.
3. Whether a hCG trigger was used
4. Number of interventions
5. Number of cycles
6. Methods of fertilisation (e.g timed intercourse, IUI)

Outcomes

1. Definition of clinical pregnancy used
2. Methods used to assess all outcomes
3. The number of started and completed cycles for each treatment modality.
4. The number of clinical pregnancies (total and ongoing).
5. The number of cycles with OHSS.
6. The number of multiple births.
7. The number of miscarriages.

Multiple births included the delivery of two or more babies. It did not include multiple pregnancies reduced to a singleton during fetal development. Miscarriages included all pregnancy losses prior to a gestation of 20 completed weeks, not the reduction of multiples during fetal development.

Assessment of risk of bias in included studies

The risk of bias of all studies which were deemed eligible for the review were then assessed independently by the two reviewers (Nat Athaullah and Michelle Proctor), with discrepancies to be resolved by discussion.

The standard checklist created by the MDSG was used.

Section i: Internal Validity
1)Was the assigned treatment adequately concealed prior to allocation?
2)Were the outcomes of participants who withdrew or were excluded after allocation described and included in an "intention to treat" analysis?
3)Were the outcome assessors blind to assignment status?
4)Were the treatment and control group comparable at entry?
5)Were the participants blind to assignment status following allocation?
6)Were the treatment providers blind to assignment status?
7)Were the care programmes, other than the trial options, identical?
8)Were the withdrawals <10% of the study population
Section ii: External Validity
9)Were the inclusion and exclusion criteria for entry clearly defined?
10)Were the outcome measures used clearly defined?
11)Were the accuracy, precision, and observer variation of the outcome measures adequate?
12)Was the timing of the outcome measures appropriate?
The quality of allocation concealment was graded as either adequate (A), unclear (B), or inadequate (C), following the detailed descriptions of these categories provided by the Menstrual Disorders and Subfertility Review Group.
It was intended to use this information in investigation of any heterogeneity and in sensitivity analyses. Other aspects of study quality including the extent of blinding (if appropriate), whether groups were comparable at baseline, the extent of losses to follow-up, participation levels, whether the outcome assessment standardised, and whether an "intention to treat" analysis was undertaken, was also assessed. This information is presented in a table describing the included studies and will provide a context for discussing the reliability of the results.

RESULTS

Description of studies

Thirty-two studies were identified which potentially fitted the stated inclusion criteria. Further investigation showed five were adequate for inclusion in this review. All of the trials described treatment with clomiphene - no trials with the use of tamoxifen were found. All five trials compared clomiphene with either hMG or r-FSH. None of the included trials mentioned the use of donor sperm.
STUDIES EXCLUDED FROM THE REVIEW
See Characteristics of excluded studies
Twenty-seven trials were excluded from the review. The reasons for exclusion of these trials are summarised in the table of characteristics of excluded studies.
STUDIES INCLUDED IN THE REVIEW
See Characteristics of included studies
Five trials were included in the review. Four trials were of parallel design, one was of cross-over design (Ecochard 2000). All described themselves as random, although four did not state how randomisation was achieved. Three compared clomiphene with hMG (Ecochard 2000; Karlstrom 1993; Karlstrom 1998), one with high-purity urinary gonadotrophin (Balasch 1994) and one with r-FSH (Nakajima 1999). Two trials were performed in Sweden and one apiece in USA, Canada, Spain and France.
All the trials included couples diagnosed with unexplained subfertility, though two had not clearly discussed how they reached this diagnosis. Only 231 of the 695 couples in the five trials could be clearly identified as having unexplained subfertility. There were a variety of different clomiphene and gonadotrophin regimens, which differed between each group. In all six of the studies a hCG trigger injection was used to induce ovulation - in three trials this was used for both treatment regimes (Balasch 1994; Ecochard 2000; Manganiello 1997) and in three trials only the gonadotrophin group received the trigger injection (Karlstrom 1993; Karlstrom 1998; Nakajima 1999).
Balasch 1994 - CC versus high purity urinary gonadotrophins
Women were randomised to receive two cycles of either clomiphene citrate (CC) or high purity urinary gonadotrophins. The study consisted of 100 participants (60 with male factor and 40 with unexplained subfertility, although the results from the couples with male factor were not included in this review). The diagnosis of unexplained subfertility was stated. The average age of the women was given. For those in the CC group, 50 mg was given on day 5-9, whilst those in the high purity urinary gonadotrophins group received 75 IU from day 7 until follicular maturation. In both groups a trigger of 10,000 IU hCG was given when the leading follicle was >=17 mm. In both groups the women were inseminated by IUI. Pregnancy was diagnosed by ultrasound. Details regarding pregnancy rate and miscarriages were given. There was no mention of multiple births or OHSS.
The author was contacted for additional information and a reply was received. Randomisation was achieved via computerised allocation. Treatment was unblinded. 20 women with unexplained subfertility were randomised to receive CC+IUI and 20 women with unexplained subfertility were randomised to receive high purity urinary gonadotrophins+IUI. There were no multiple births, miscarriages or OHSS cases.
Ecochard 2000 - CC versus hMG
Women were randomised to receive two cycles of CC or hMG. After this, the protocols were reversed, with the participants receiving the other treatment . The study consisted of 58 participants, 12 of whom had unexplained subfertility. How this diagnosis was made was also stated. Women over the age of 39 were

excluded from treatment. The CC protocol was 50-100 mg/day from days 3-7 of the cycle. The hMG protocol was 150 IU on days 4, 6, 8 and 9. Ovulation was triggered with 5,000 IU hCG when the leading follicle was >=16 mm. In both groups women were then inseminated by IUI. Pregnancy was diagnosed both by serum beta-hCG and transvaginal ultrasound. Details regarding cancelled cycles, miscarriage rate and fecundity rate were given. No detail with regard to OHSS incidence was stated.

The author was contacted for additional information and a reply was received. There were 12 women diagnosed with unexplained subfertility and only these were included in this review. Six were randomised to two cycles of CC then two cycles of hMG and six were randomised to two cycles of hMG then two cycles of CC. Results before cross-over were considered for the meta-analysis. Data for live births, pregnancy, miscarriage and multiple births were found.

Karlstrom 1993 - CC versus hMG + hCG trigger

Women were randomised to receive either CC or hMG. 157 women took part in the study, of whom 148 were analysed (76 received hMG and 72 received CC). The diagnosis of unexplained subfertility was given, though the study did not include women over the age of 39. The dosage of hMG was 150 IU given on days 2-4. CC dosage was given as 100 mg on days 3-5. The hCG trigger was only given in the hMG subgroup, CC relying on urinary LH surge. This was followed by IUI or direct intraperitoneal sperm injection (DIPI). How pregnancy was diagnosed was not stated. Data on pregnancy rate, multiple birth occurrence, miscarriage rate and OHSS were stated.

Karlstrom 1998 - CC versus hMG + hCG trigger

Information regarding this trial is from an abstract. The full text has been requested from the authors.

Women were randomised to receive either hMG or CC. 353 couples with unexplained subfertility, male factor infertility, cervical factor or mild endometriosis were randomised, of which 321 couples completed treatment. Half of the women were treated daily (no start day given) with 150 IU hMG. The other half of the women received CC for 5 days (again no start day given). The hMG group received a hCG trigger when the follicle reached 17 mm. The CC group's ovulation was timed with urinary LH. After this, women were then randomised to receive either IUI, direct intraperitoneal insemination (DIPI) or a combination of the two. Pregnancy rate per woman was reported. Information on multiple births, miscarriage rate and OHSS were not reported by the trial.

Nakajima 1999 - CC versus r-FSH +hCG trigger

Information regarding this trial is from an abstract. The full text has been requested from the authors.

Women were randomised to receive CC or r-FSH. 22 women were received four cycles of the treatment they were randomised to in alternate months (i.e. one cycle of treatment, one rest cycle, one cycle of treatment etc instead of four continuous cycles of CC or r-FSH). The diagnosis of unexplained subfertility was not clearly given, however the abstract stated that women had undergone "complete investigation" and had been infertile for at least 18 months. Dosages and regimens for both treatments were not given. Ovulation in the CC group was timed with urinary LH, whereas in the r-FSH group, ovulation was induced with hCG (dosage not given). Data on pregnancy rate, miscarriage rate, multiple birth frequency and OHSS frequency were given.

Risk of bias in included studies

RANDOMISATION TO MEDICATION PROTOCOL

All of the included studies were stated to be randomised trials. Three of the studies did not mention how they achieved randomisation (Nakajima 1999; Karlstrom 1993; Karlstrom 1998). Ecochard 2000 used opaque envelopes and a random numbers table. From correspondence it was determined that Balasch 1994 used computerised allocation. Thus in summary, we have scored the following studies accordingly (From criteria stated in the Methods of the Review):

A - Balasch 1994; Ecochard 2000

B - Karlstrom 1993; Karlstrom 1998; Nakajima 1999

BLINDING

From correspondence, Balasch 1994 was an unblinded study. The degree of blinding was unclear in the other four included studies.

INTENTION-TO-TREAT ANALYSIS AND WITHDRAWALS

Only one of the included studies mentioned an intention to treat analysis (Ecochard 2000), 7/97 cycles of CC (7.2%) and 2/86 hMG cycles (2%) had to be cancelled in this trial but analysis was performed with and without these cycles. Studies which stated where women did not complete treatment were Karlstrom 1993; Karlstrom 1998; and Nakajima 1999, the percentage dropout rates being 7.0%, 9.1%, and 9.1% respectively (these figures are withdrawals of the whole trial not just the subset with unexplained subfertility only). There were no dropouts from the Balasch 1994 study (from correspondence). Reasons for the dropout rates were given in Karlstrom 1993.

POWER CALCULATIONS

Only one on the included trials mentioned doing a power calculation (Ecochard 2000). Ecochard calculated that they needed to include 224 cycles of treatment to show a difference between the two treatments at 80% power (alpha = 0.05), assuming that fecundity was 10% and that hMG increased that to 25%. This trial only completed 174 cycles (58 women, although only 12 had unexplained subfertility) so statistical power was not reached.

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BASELINE SIMILARITY OF THE GROUPS

(1) AGE

The average age of participants was given in all but two of the studies (Karlstrom 1998; Nakajima 1999 - both abstracts). The average age of the women receiving each intervention was within one standard deviation of each other.

(2) DIAGNOSIS OF UNEXPLAINED SUBFERTILITY.

Four studies stated how they diagnosed unexplained subfertility. The criteria of this review stated that the preferred diagnosis involved looking for proof of tubal patency (hysterosalpingogram or laparoscopy), normal ovulatory function (basal body temperature, cervical mucus changes, LH testing of serum and mid-luteal progesterone) and normal semen analysis (WHO criteria).

These criteria were fulfilled by two studies - (Balasch 1994; Karlstrom 1993). Ecochard 2000 mentioned that not all of the women received both a hysterosalpingogram and a laparoscopy. Karlstrom 1998 and Nakajima 1999 did not mention the diagnostic criteria at all, but again they were abstracts. The Karlstrom 1998 abstract, mentioned that they had similar protocols to the Karlstrom 1993 paper.

(3) CLOMIPHENE AND GONADOTROPHIN PROTOCOLS.

None of the trials used an identical regimen with regard to the treatment that was being prescribed. Where stated, dosages of clomiphene ranging from 50 mg-150 mg were used. These were given for five days in all six of the trials, although the start day was anywhere from before day one of the menstrual cycle through to day five. hMG was given in dosages of 150 IU, though the dosage was given either continuously for five days, starting either on day 2-4 or every other day from day four. See the Description of Studies section for more details on the protocols used by individual trials.

(4) THE USE OF A HCG TRIGGER

All but one of the included trials used a hCG trigger. In trials where the dosage was stated, hCG was given as 5000-10000 IU when the follicles were between 16-19 mm. Every group received a hCG trigger except for the clomiphene treated groups in three studies (Karlstrom 1993; Karlstrom 1998; Nakajima 1999). The hCG trigger is a crucial co-intervention in these three trials and the assessed intervention in the case of these trials becomes clomiphene versus gonadotrophins plus the hCG trigger.

Effects of interventions

Overall five studies were selected which compared anti-oestrogens with gonadotrophins. No studies were found comparing either anti-oestrogens or gonadotrophins in unity with combination.

Of the pre-specified sub-group meta-analyses, trials comparing anti-oestrogens to different types of gonadotrophins, and trials where the co-intervention of hCG trigger was used in only the gonadotrophin group and not the clomiphene group (a potentially influential co-intervention), were analysed as sub-groups.

LIVE BIRTH PER COUPLE

Two studies, both comparing CC versus hMG, provided data on 15 live births (Ecochard 2000; Karlstrom 1993). The results as a whole were not statistically significant (Peto OR 0.51, 95% CI 0.18 to 1.47). The analysis was dominated by the results of Karlstrom 1993, as the pre-crossover results from Ecochard 2000 did not produce a live birth for either protocol.

Although the meta-analysis did not use the results from the post-crossover phase of the Ecochard 2000 trial, it should be noted that there was one live birth out of 12 randomised participants. It occurred in the hMG phase of stimulation in a protocol involving two cycles of CC followed by two cycles of hMG.

Balasch 1994 stipulated that there were six pregnancies but there were no miscarriages. Though presumably all the pregnancies went on to produce live births, this review cannot accept such a presumption.

PREGNANCY RATE PER WOMAN

Three studies, two comparing CC versus hMG and one comparing CC versus high purity urinary gonadotrophins, were identified which reported the pregnancy rate per woman. The results as a whole were statistically significant with the hMG group showing a higher pregnancy rate (Peto OR 0.44 95% CI 0.19 to 0.99). The analysis was dominated by the results of Karlstrom 1993 which included 148 of the 200 women included in this comparison. The sub-group of anti-oestrogens versus hMG, which included two studies (Ecochard 2000; Karlstrom 1993) showed no significant difference (Peto OR 0.54, 95% CI 0.21 to 1.37). The one study comparing clomiphene with high purity urinary gonadotrophins (Balasch 1994) also showed no significant difference (Peto OR 0.22 95% CI 0.04 to1.20). No trials reported pregnancy rate per woman (stated or otherwise) for studies which compared clomiphene with recombinant FSH.

When the meta-analysis was repeated excluding the trials with a hCG co-intervention in only the gonadotrophin group (Karlstrom 1993; Nakajima 1999), the results were not statistically significant (Peto OR 0.33 95% CI 0.09 to1.20). For CC hMG (Ecochard 2000), there was no statistical difference (Peto OR 7.39 95% CI 0.15 to 372.41). For CC vs high purity urinary gonadotrophins (Balasch 1994), there was also no statistical difference (Peto OR 0.22 95% CI 0.04 to1.20).

Although the meta-analysis did not use the results from the post-crossover phase for the Ecochard 2000 trial, it should be noted that there were two pregnancies out of 12 randomised participants. One occurred in the post-crossover clomiphene phase and the other in the post-crossover hMG phase of respective protocols.

PREGNANCY RATE PER CYCLE

Data per couple are required for meaningful comparison, however pregnancy per cycle is reported more often in subfertility research. Reported numbers are given for information in the graphs, but it should be noted that the apparent confidence intervals may be incorrect and that pooling the reported figures would be inappropriate

Five trials were identified which reported pregnancy rate per cycle. The confidence intervals of all five trials crossed the line of no effect, however the mean pregnancy rate of the clomiphene group was only 8% compared to 25% with gonadotrophins, indicating that a benefit associated with gonadotrophins. Similarly, no levels of significance were detected for any of the subgroups.

Although the analysis did not use the results from the post-

crossover phase of the Ecochard 2000 trial, it should be noted that there were two pregnancies in 36 cycles of treatment. One occurred in the post-crossover clomiphene phase and the other in the post-crossover hMG phase of respective protocols.

MISCARRIAGE RATE PER PREGNANCY

Three trials, one comparing CC versus hMG, one comparing CC versus high purity urinary gonadotrophins and one comparing CC with rFSH, were identified which detailed miscarriage rate per pregnancy (for the purposes of this meta-analysis, defined as a woman being clinically pregnant who does not deliver a live baby). The results as a whole were not statistically significant (Peto OR 0.46 95% CI 0.06 to 3.33). The subgroup comparing anti-oestrogens with hMG was also not statistically significant (Peto OR 0.69 95% CI 0.07 to 6.99). In this group it should also be noted that in the pre-crossover results for the Ecochard 2000 trial, there was one miscarriage in the CC group, but this was not included in the meta-analysis because there were no pregnancies in the hMG group. There were no miscarriages in either group in the study comparing anti-oestrogens with high purity urinary gonadotrophins (Balasch 1994). The one study comparing anti-oestrogens with recombinant FSH (Nakajima 1999) showed no statistical significance (Peto OR 0.14 95% CI 0.00 to 6.82).

When the meta-analysis was repeated excluding the trials with a co-intervention hCG trigger only in the gonadotrophin group (Karlstrom 1993; Nakajima 1999), there were insufficient data for statistical analysis to be feasible.

Although the meta-analysis did not use the results from the post-crossover phase of the Ecochard 2000 trial, it should be noted that, of the two pregnancies, one miscarried. This occurred from a post-crossover clomiphene phase.

MULTIPLE BIRTH RATE PER PREGNANCY

Three trials were identified, one comparing CC versus hMG, one comparing CC versus high purity urinary gonadotrophins and one comparing CC with rFSH, which detailed the multiple birth rate (a woman who delivers two or more babies in the one pregnancy). The results as a whole were not statistically significant (Peto OR 0.37 95% CI 0.06 to 2.43). All subgroups were also not statistical significant.

When the meta-analysis was repeated excluding the trials with a co-intervention hCG trigger only in the gonadotrophin group (Karlstrom 1993; Nakajima 1999), there were insufficient data for statistical analysis to be feasible.

OCCURRENCE OF OHSS

None of the included trials reported any cases of ovarian hyperstimulation syndrome and thus statistics could not be generated.

OCCURRENCE OF OVERSTIMULATION LEADING TO DISCONTINUATION OF THE CYCLE

None of the included trials reported any cases of cancelled cycles owing to overstimulation and thus statistics could not be generated.

SENSITIVITY ANALYSIS

A sensitivity analysis was to be performed if there were more than ten trials, on criteria stated above. However only five trials were included in the meta-analysis.

DISCUSSION

When trials with important co-interventions were excluded from the meta-analysis, no significant differences were apparent between gonadotrophins and anti-oestrogens for the primary outcomes. Even without exclusions, the meta-analysis had insufficient power to detect a clinically significant difference. For example a single study would require analysed data from over 300 participants to have 80% power to detect a possible doubling of the pregnancy rate. (see meta-analysis graph for comparison 02, anti-oestrogens versus gonadotrophins, excluding trials with hCG trigger co-intervention; outcome 02, pregnancy rate per womanAnalysis 2.1),

.

There are a number of important considerations as follows.

1. METHODOLOGICAL COMMENTS

The meta-analysis gave a high weighting to one study (Karlstrom 1993), due to its large sample size. However this study had weakness in its methodology (for its use in this meta-analysis), which has been previously stated in another meta-analysis (Gallot-Lavallee 1995). Ovulation was triggered in their hMG protocol, whereas it was allowed to occur naturally in the CC cycles and its timing was judged with urinary LH levels. Thus the two treatment groups not only differed in their intervention alone, but also in how ovulation was triggered, which could be a major confounding factor. Karlstrom 1993 argued that for cycles stimulated with CC, urinary LH surge leads to better pregnancy outcomes than using a hCG trigger, quoting a study by Martinez 1991 as support for their argument. Thus they wanted to compare optimal CC performance with optimal hMG performance. However this Martinez 1991 trial is equally flawed, using a cross-over design without a wash-out period; in fact for this trial, results before cross-over were identical.

Furthermore:

(1) A hCG trigger had been recommended by two studies previously (Harrison 1983; Fisch 1989), though neither timed the hCG injection with follicle size on ultrasound.

(2) Plosker 1994 examined factors to increase pregnancy rate in cycles with IUI and concluded that a hCG trigger was superior to urinary timed LH levels.

(3) Several studies in our meta-analysis used a hCG trigger for its CC component.

It would be inappropriate to draw conclusions based on the results of the meta-analysis which included trials with this important co-intervention. It was thus deemed rational to repeat the meta-

analysis excluding trials which used a hCG trigger in only one arm of the trial (i.e. excluded studies were Karlstrom 1993; Karlstrom 1998; Nakajima 1999). This analysis lacked statistical power and was unable to identify whether there may be differences between anti-oestrogens and gonadotrophins for the variables examined.

The dosage of CC was different in all of the included trials. It is unclear whether the dosage makes a significant difference, though one review (Blacker 1992) suggested that a dose of 50mg would provide the highest cumulative pregnancy rates - this review was based on data from 1982. Although the dosage of hMG used was consistent, 150 IU over 5 days, the start day varied. There is no clear consensus of ideal regimens for these interventions.

None of the included trials were double blinded, inevitably allowing scope for bias. A couple being treated with clomiphene may not be observed as meticulously as those on hMG (Gallot-Lavallee 1995).

2. FINDINGS FROM OTHER RANDOMISED TRIALS.

One of our included trials used the pre-crossover data from a crossover trial (Ecochard 2000). The trial's full results concluded that there was no significant difference between CC and hMG, which did not differ from the results used in the meta-analysis. The trial differed from others in the meta-analysis as they did not adjust the dose of hMG to the size of the follicle, which was the case in other studies (e.g. Karlstrom 1993). Also a study which did not include women with unexplained subfertility (Check 1992), concluded that there was no evidence HMG leading to superior pregnancy rates when compared to clomiphene.

No trials fitting the criteria were found comparing a combination of the two drugs with either anti-oestrogen or gonadotrophin on its own. A randomised trial by Ransom 1996 was, excluded because all the women included had failed on CC. The researchers concluded that menotrophins were better on their own than CC/hMG in women who have failed under CC therapy.

3. FINDINGS FROM NON-RANDOMISED TRIALS.

There have been a number of non-randomised studies published. Karande 1995 compared CC with hMG as part of a comparison of FSH and IUI protocols and concluded that there was no statistical advantage in using one over the other. El-Sadek 1998 reported that though there was a trend favouring the use of CC/hMG over CC alone, there was no statistical difference. Plosker 1994 stated that protocols involving hMG were more likely to produce a pregnancy than those which are natural or stimulated with CC alone. Dickey 1992 also performed a retrospective analysis which drew the same conclusion.

It remains unclear whether combinations are superior to the treatments on their own.

4. SECONDARY OUTCOMES.

Though previous literature has suggested that there is more likely to be multiple pregnancies and OHSS incidence with the use of either clomiphene or gonadotrophins, this could not be demonstrated in our meta-analysis. In fact none of the trials reported any cases of OHSS.

5. OTHER POINTS OF NOTE

Each of the studies which were used in the review used a different protocol for its gonadotrophin administration. For example Ecochard 2000 used alternate day hMG administration then used the hCG trigger when the follicle was 16mm, whereas Balasch 1994 started hMG administration on day 7 and triggered at 17mm. It is clear that there is no definitive protocol for these injections, nor whether one or the other is better. If there was a sub optimal gonadotrophin administration protocol, it would skew the results

It is also important to note the other alternatives and variations to anti-oestrogens and gonadotrophins. It has been proposed that CC might not be as effective as hMG owing to its adverse effects on cervical mucus and the endometrium (Dickey(2) 1993). A recent study (Gerli 2000) suggested the use of ethinyl oestradiol with CC to reverse these effects, though this may lead to a higher miscarriage rate. Certainly further research is required.

Though beyond the scope of this review, cost is also worthy of discussion. The medications vary in price but a cycle of recombinant fsh can be twenty times that of clomiphene. Many centres use clomiphene as a first choice, however many others use FSH and other injectable agents as their primary agent. These decisions are often not evidence based but are due to individual clinical preference. Guzick 1998 performed a retrospective analysis which attempted to calculate cost per pregnancy. This suggested that though gonadotrophins were more likely to produce pregnancy, the cost per pregnancy was less in the clomiphene group as opposed to the gonadotrophin group, i.e. clomiphene was more cost effective. However they also concluded that randomised controlled trials comparing the two agents were necessary to provide more definitive information (Guzick 1998).

In 1995 a meta-analysis comparing CC and hMG was published (Gallot-Lavallee 1995), which could only locate three randomised trials. It concluded that hMG may be better than CC, but this may be a consequence of better monitoring and perhaps an increased incidence of multiple pregnancies. The Gallot-Lavallee 1995 meta-analysis included the findings of both randomised and non-randomised studies, although statistical analysis was not performed because of the use of non-randomised populations. Although it involved a similar search strategy to ours, other differences were the inclusion of a comparison with placebo and no policy of exclusion or inclusion of trials based upon methodological quality. Our meta-analysis, six year's after the Gallot-Lavallee 1995 meta-analysis and with more stringent inclusion criteria, has failed to demonstrate conclusively which should be the treatment of choice.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence that the use of oral versus injectable ovulation induction rates gives rise to differences in pregnancy or live birth rates in unexplained subfertility. Preference and cost of treatment will be other influential factors governing the decision of which agent to use.

Implications for research

Further RCTs of sufficient quality and power (numbering more than 300 participants) are needed to answer this question. The challenge for those who promote the use of gonadotrophins in this context is to demonstrate their benefit in a randomised trial. Such a trial should be preceded by ascertainment of the optimal dose regimes of oral and injectable ovulation induction agents in the context of unexplained infertility. It is likely to benefit from a multi-centre approach and must be free from bias introduced by co-interventions or differential monitoring. Trials should report outcome data as a live birth rate 'survival' analysis. Ideally the trials should have the same universal protocols for both its arms. If the more expensive, injectable agents are proven to be beneficial, maybe in certain health care systems, funding for their usage will be granted.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Balasch 1994

Methods	Parallel trial Method of randomisation: not stated, author contacted: computerisation Blinding: unclear (author contacted: Non) 100 participants (60MF, 40UI) Women were randomised to receive two cycles of CC and IUI or two cycles of high purity urinary gonadotrophins and IUI (For UI 20 received CC and 20 received high purity urinary gonadotrophins) Intention to treat analysis: unknown
Participants	Inclusion: MF(WHO criteria). US. Exclusion criteria: None stated. Diagnosis of US, (after BBT, mid-luteal progesterone, prolactin, oestrogen, post-coital test, HSP and lap. , of length >= 2years) Age: 32.6+-2.9 CC, 31.8+-3.2 'FSH' Duration of infertility: mean (std dev for those with male factor or unexplained, CC 6.1 (2.3) years vs FSH 5.1 (2.5) years Location: University Hospital, Barcelona, Spain
Interventions	1.CC 50mg on day 5-9 2.High purity urinary gonadotrophin 75IU from day 7 till maturation. Ovulation triggered with 10000 IU hCG when follicle >=17mm. 1500IU hCG given 4, 7 and 10 days after ovulatory dose to supplement luteal phase in all women. Then IUI 35-36hrs after. Not intercourse 3 days before semen collection Each woman received 2 cycles of treatment.
Outcomes	Preg: diagnosed by U/S Pregnancies: CC - 2/50 ongoing, 2/50 miscarried. 'FSH' 11/50 ongoing, 1/50 aborted PR/cycle MF:CC 3/58, 'FSH' 7/56 UI CC 1/40, 'FSH' 5/38. No OHSS were reported. No multiples mentioned. (author contacted: No reported miscarriages nor multiples)
Notes	Author contacted and replied. No of women: 40 UI, 20 received CC, 20 received high purity urinary gonadotrophins. No miscarriages, no multiple births. Method of randomisation: Computerisation No blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ecochard 2000

Methods	Cross over trial. Method of randomization: Opaque envelope and random numbers table Blinding: unclear 58 patients, 33MF, 12 idiopathic (unexplained), 13 female factor infertility. 6 randomised to CCHH, 6 randomised to HHCC Intention to treat analysis performed on cycle data. 7/97 cycles CC stopped, 2/86 cycles hMG stopped. Reasons given. Sources of Funding: French Ministry of Health
Participants	Inclusion criteria: Trial included male and female factor infertility and unexplained subfertility. Complete infertility evaluation was performed Exclusion: >39, previous treatment, anovulation, azoospermia, uncorrected tubal disease, previous unsuccessful use of CC or hMG or contraindications to treatment.. Diagnosis of unexplained subfertility: Infertility >24 months, normal ovulatory cycles, semen analysis (WHO criteria), endometrial biopsy, HSP, PCT and diagnostic laparoscopy. Average age CC 30.4+-3.5, hMG 31.5+-3.7 Duration of infertility: mean (std dev), CC 4.0 (2) years, hMG 3.3 (2) years Location: University teaching hospital, Lyon, France
Interventions	1.CC 50-100mg/d in days 3-7 2.hMG 150IU on days 4, 6, 8 and 9 Ovulation then triggered with 5000IU hCG when follicle >=16mm. IUI 36 hrs after ovulation or 24 hrs after LH surge + hCG. Two treatment groups - Group 1:CC for 2 cycles then hMG for 2 cycles. Group 2:hMG for 2 cycles then CC for 2 cycles
Outcomes	Clinical Pregnancy (positive beta-hCG and transvaginal U/S 2 & 4 weeks later). Cancelled cycles, number of preovulatory follicles (means and SD) Total motile sperm count Cycle fecundity rate Cumulative pregnancy rate Miscarriage rate No OHSS reported.
Notes	Author contacted and replied. Twelve women with UI randomised, six apiece to CCHH and HHCC. Data pre and post cross over was generated fro live birth, pregnancy, miscarriage and multiple birth rate

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Karlstrom 1993

Methods	Parallel trial Method of Randomisation: Unstated (women randomised to one of eight treatment groups) Blinding: unstated 157 women randomised, 148 analysed (76hMG, 72 CC) Intentio-to-treat analysis: not stated
Participants	Inclusion:US>2yrs(method of assessment given), <39, no previous treatment, normal sperm. Exclusion criteria: non stated. Diagnosis of US: as above Average age CC 31.7 (range 21 to 38), hMG 32 (range 22 to 38) Duration of infertility: average (range, CC 5.1 (2 to 14) years vs hMG 4.9 (2 to11) years Location: Uppsala Univeristy Hospital,Sweden
Interventions	1.hMG 150IU on days 2-4. 2.CC 100mg on days 3-5 of cycle. hCG trigger only in the hMG group, 10000IU when follicle was >=17mm. Otherwise a urinary LH surge detected for CC group. Followed by IUI or DIPI or IUI or instructed to two nights intercourse. IUI/IPSI 36-41 hrs after hCG or same day as LH surge
Outcomes	Clinical Pregnancy 13/76 hMG pregnant (6 multips, 5 pairs of twins and 1 triplets) 1 triplets-twins, 1 twins-single, 1 single-miscarry, 2 miscarriages. 6/72 CC (1 twins) (No miscarriages, but 1 miscarried later).No cases of OHSS stated.
Notes	An attempt was made to contact the authors, but no reply was granted

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Karlstrom 1998

Methods	Parallel trial Method of randomisation: Unstated Blinding: Non stated Intention to treat: unstated. 353 women randomised, 321 completed treatment. Dropout reasons not given, Intention to Treat Analysis not stated
Participants	Inclusion: US (method of assessment not stated), mild endometriosis, cervical factor or male factor. Age of women: not stated. Duration of infertility: not stated. Location Uppsala University Hospial, Sweden

Karlstrom 1998 (*Continued*)

Interventions	1. hMG 150IU daily until leading follicle 17mm. (start day not stated), followed by hCG(dosage not stated) when leading follicle >=17mm. 2.CC 100mg for 5 days(start day not stated). Ovulation predicted by urinary LH Ovulatory trigger with hCG (dosage unstated) only in the hMG group. Followed by IUI or DIPI or combination of both 38 hrs after. Or followed by intercourse on day of hCG injection or day of LH surge for two nights
Outcomes	hMG 26/159 CC 19/162 Data on multiple births, OHSS, miscarriage rate not given.
Notes	An attempt was made to contact the authors but no reply was granted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Nakajima 1999

Methods	Parallel trial Method of Randomisation: Unknown 22 participants, 20 analysed, two withdrawals (no reason given). Intention to treat analysis not stated. Sources of Funding - Query Serono, Novartis and Berry Technologies, who all contributed materials. Blinding: Unknown
Participants	Inclusion Criteria: US Diagnosis of US: (complete investigation stated, but no further details given) Average ages: not stated Duration of infertility: minimum 18 months Location Alberta, Canada.
Interventions	1.CC + IUI 2.rFSH + IUI Dosages not given. IUI timed with urinary prediction kit in CC group and 28-36 hours after hCG in rFSH group (hCG dosage and timing not stated)
Outcomes	CC - 4/27 (2 single, 1 twins at 33 weeks) FSH - 4/28 (4 singleton) No serious SE's, 1 pt from each withdrew.
Notes	An attempt was made to contact researchers, but no reply was granted

Risk of bias

Nakajima 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

MF = Male Factor Infertility, US=Unexplained subfertility, CC=Clomiphene Citrate, IUI = Intrauterine Insemination, FSH = Follicle Stimulating Hormone, BBT = Basal Body Temperature, HSP = Hysterosalpingogram, hCG = human chorionic gonadotrophin, PR = Pregnancy Rate, OHSS = Ovarian Hyperstimulation Syndrome. CCHH = 2 cycles of clomiphene and then two cycles of hMG. HHCC = two cycles of hMG than two cycles of clomiphene. hMG = human Maternal Gonadotrophin, U/S = ultrasound. LH = luteinising hormone. DIPI = Direct intraperitoneal insemination. SE=side effects.

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

Study	Reason for exclusion
Abdalla 1990	Compared CC/hMG and buserelin/hmg
Ahmed-Ebbiary 1995	Not randomised wrt ovulation protocols
Arcaini 1996	Did not compare superovulation protocols
Arici 1994	Compared CC/hCG with urinary timed LH
Check 1992	Mixed interventions in both groups
Dhont 1995	Compared CC/hMG with GnRH/hMG
Dickey 1992	Retrospective analysis
Dickey(2) 1993	Retrospective analysis
El-Sadek 1998	Not randomised for CC or CC/hMG protocols
Fanchin 1995	Not random with induction protocols
Fisch 1989	Compared CC with placebo
Frederick 1994	Retrospective analysis
Gerli 2000	Compared CC with CC and oestrogen
Grochowski 1998	compared CC/hMG with d-triptorelin/hMG
Harrison 1983	Compared CC with CC/hCG

(*Continued*)

Karande 1995	Not randomised for the CC or hMG protocols
Kingsland 1992	Intervention for IVF
Lidor 2000	Non randomised study
Manganiello 1997	No mention of randomisation, participants allocated sequentially
Martinez 1991	Compared CC with CC/hCG for IUI
Nuojua-Huttunen 1997	Compared IUI with FSP after hCG administration
Plosker 1994	Retrospective analysis
Polson 1991	Compared hMG/buserelin and buserelin/hMG
Quigley 1984	Did not include couples with unexplained infertility
Ransom 1996	Previous treatment with CC for all patients
Rogers 1986	Compared different CC/hMG protocols
Van der Auwera 1994	Interventions for IVF treatment

DATA AND ANALYSES

Comparison 1. Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth per couple	2	160	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.18, 1.47]
1.1 Clomiphene vs human maternal gonadotrophins (hMG)	2	160	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.18, 1.47]
1.2 Clomiphene vs high purity urinary gonadotrophins	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Clomiphene vs recombinant FSH	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pregnancy rate per woman	3	200	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.19, 0.99]
2.1 Clomiphene vs human maternal gonadotrophins (hMG)	2	160	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.21, 1.37]
2.2 Clomiphene vs high purity gonadotrophin	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.04, 1.20]
2.3 Clomiphene vs recombinant FSH	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Pregnancy rate per cycle	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3.1 Clomiphene vs human maternal gonadotrophins (hMG)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Clomiphene vs high purity gonadotrophin	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Clomiphene vs recombinant FSH	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Miscarriage rate per pregnancy	3	33	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.06, 3.33]
4.1 Clomiphene vs human maternal gonadotrophins (hMG)	1	19	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.07, 6.99]
4.2 Clomiphene vs high purity urinary gonadotrophin	1	6	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Clomiphene vs recombinant FSH	1	8	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
5 Multiple birth rate per pregnancy	3	33	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.06, 2.43]
5.1 Clomiphene vs human maternal gonadotrophins (hMG)	1	19	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.06, 4.26]
5.2 Clomiphene vs high purity urinary gonadotrophin	1	6	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Clomiphene vs recombinant FSH	1	8	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]

6 Occurrence of overstimulation leading to discontinuation of the study per cycle	3	281	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 Clomiphene vs human maternal gonadotrophins (hMG)	1	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Clomiphene vs high purity urinary gonadotrophin	1	78	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Clomiphene vs recombinant FSH	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Anti-oestrogens vs gonadotrophins (excluding trials with hCG trigger co-intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy rate per woman	2	52	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.08, 1.84]
1.1 Clomiphene vs human maternal gonadotrophins (hMG)	1	12	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
1.2 Clomiphene vs high purity urinary gonadotrophin	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.04, 1.20]
1.3 Clomiphene vs recombinant FSH	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pregnancy rate per cycle	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
2.1 Clomiphene vs human maternal gonadotrophins (hMG)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Clomiphene vs high purity urinary gonadotrophin	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Clomiphene vs recombinant FSH	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

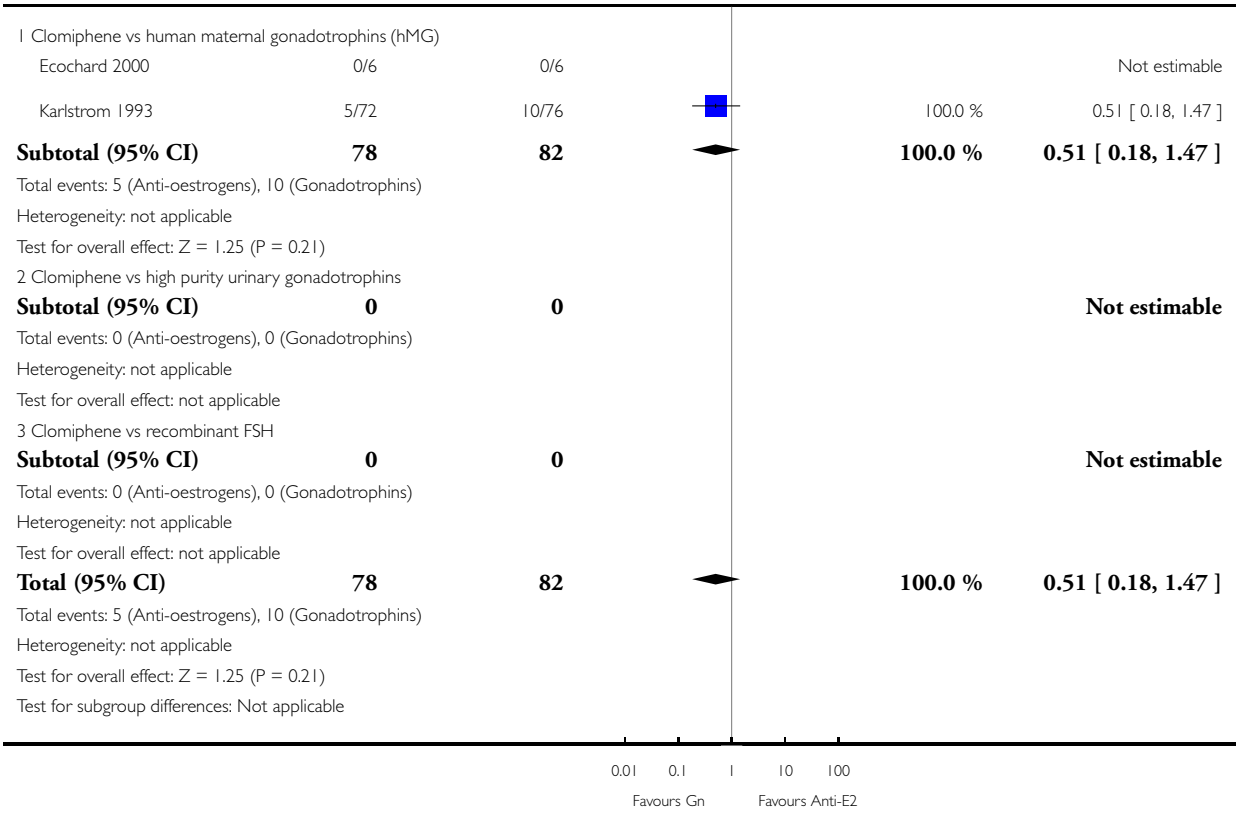
Analysis 1.1. Comparison 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention), Outcome 1 Live birth per couple.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention)

Outcome: 1 Live birth per couple

Study or subgroup	Anti-oestrogens n/N	Gonadotrophins n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Clomiphene vs human maternal gonadotrophins (hMG)					
Ecochard 2000	0/6	0/6			Not estimable
Karlstrom 1993	5/72	10/76		100.0 %	0.51 [0.18, 1.47]
Subtotal (95% CI)	**78**	**82**		**100.0 %**	**0.51 [0.18, 1.47]**
Total events: 5 (Anti-oestrogens), 10 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
2 Clomiphene vs high purity urinary gonadotrophins					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Clomiphene vs recombinant FSH					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**78**	**82**		**100.0 %**	**0.51 [0.18, 1.47]**
Total events: 5 (Anti-oestrogens), 10 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Not applicable					

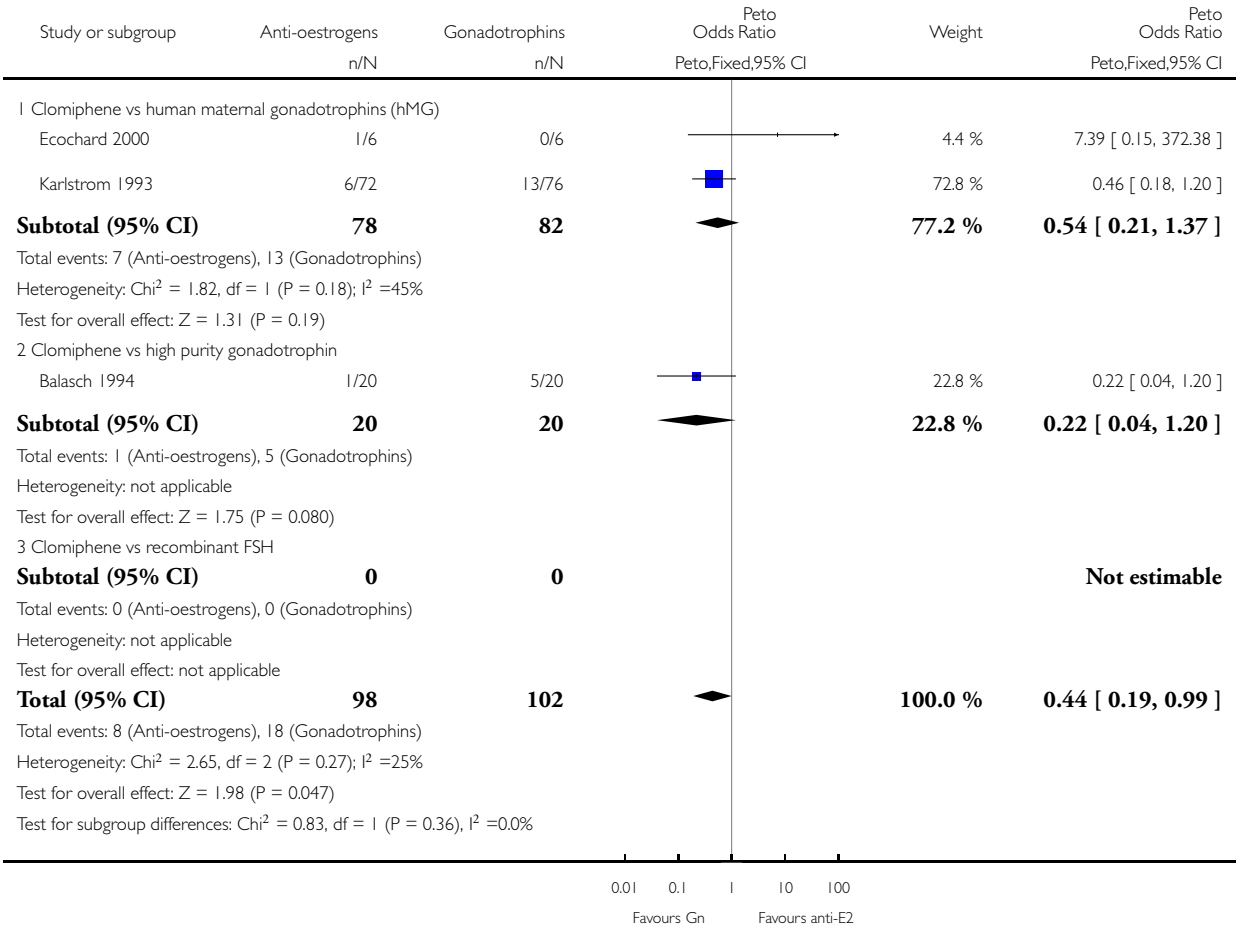


Analysis 1.2. Comparison 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention), Outcome 2 Pregnancy rate per woman.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention)

Outcome: 2 Pregnancy rate per woman



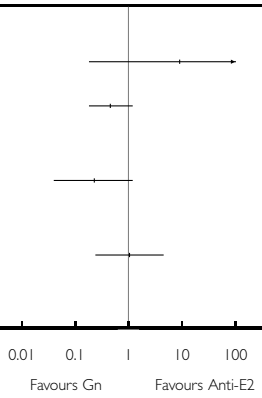
Analysis 1.3. Comparison 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention), Outcome 3 Pregnancy rate per cycle.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention)

Outcome: 3 Pregnancy rate per cycle

Study or subgroup	Anti-oestrogens n/N	Gonadotrophins n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Clomiphene vs human maternal gonadotrophins (hMG)				
Ecochard 2000	1/10	0/12		9.03 [0.18, 462.31]
Karlstrom 1993	6/72	13/76		0.46 [0.18, 1.20]
2 Clomiphene vs high purity gonadotrophin				
Balasch 1994	1/40	5/38		0.23 [0.04, 1.19]
3 Clomiphene vs recombinant FSH				
Nakajima 1999	4/27	4/28		1.04 [0.24, 4.61]

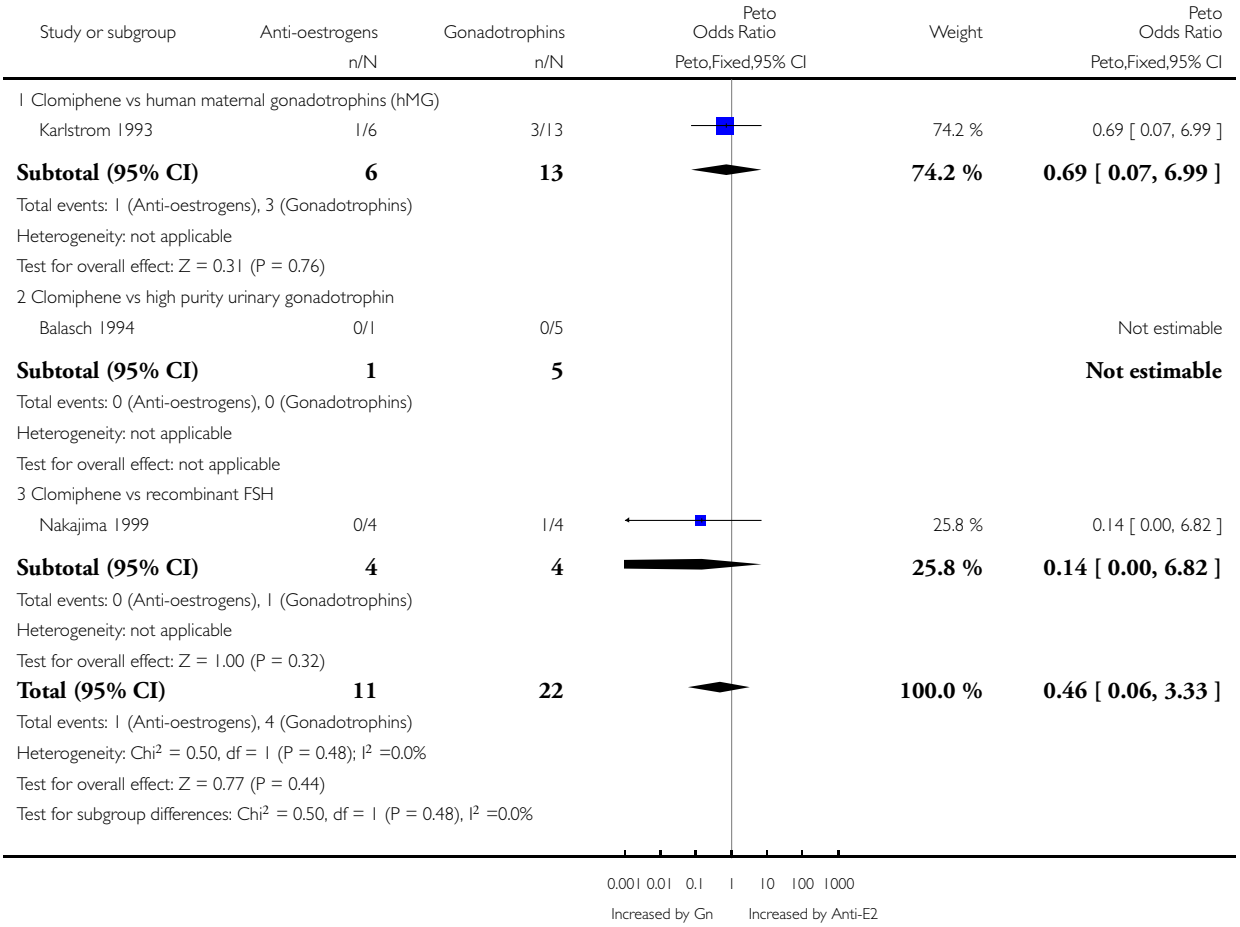


Analysis 1.4. Comparison 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention), Outcome 4 Miscarriage rate per pregnancy.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention)

Outcome: 4 Miscarriage rate per pregnancy



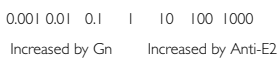
Analysis 1.5. Comparison 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention), Outcome 5 Multiple birth rate per pregnancy.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention)

Outcome: 5 Multiple birth rate per pregnancy

Study or subgroup	Anit-oestrogens n/N	Gonadotrophins n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Clomiphene vs human maternal gonadotrophins (hMG)					
Karlstrom 1993	1/6	4/13		77.1 %	0.50 [0.06, 4.26]
Subtotal (95% CI)	**6**	**13**		**77.1 %**	**0.50 [0.06, 4.26]**
Total events: 1 (Anit-oestrogens), 4 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
2 Clomiphene vs high purity urinary gonadotrophin					
Balasch 1994	0/1	0/5			Not estimable
Subtotal (95% CI)	**1**	**5**			**Not estimable**
Total events: 0 (Anit-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Clomiphene vs recombinant FSH					
Nakajima 1999	0/4	1/4		22.9 %	0.14 [0.00, 6.82]
Subtotal (95% CI)	**4**	**4**		**22.9 %**	**0.14 [0.00, 6.82]**
Total events: 0 (Anit-oestrogens), 1 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
Total (95% CI)	**11**	**22**		**100.0 %**	**0.37 [0.06, 2.43]**
Total events: 1 (Anit-oestrogens), 5 (Gonadotrophins)					
Heterogeneity: Chi^2 = 0.33, df = 1 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 1.03 (P = 0.30)					
Test for subgroup differences: Chi^2 = 0.33, df = 1 (P = 0.56), I^2 =0.0%					



Analysis 1.6. Comparison 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention), Outcome 6 Occurrence of overstimulation leading to discontinuation of the study per cycle.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 1 Anti-oestrogens vs gonadotrophins (including trials with hCG trigger co-intervention)

Outcome: 6 Occurrence of overstimulation leading to discontinuation of the study per cycle

Study or subgroup	Anti-oestrogens n/N	Gonadotrophins n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Clomiphene vs human maternal gonadotrophins (hMG)					
Karlstrom 1993	0/72	0/76			Not estimable
Subtotal (95% CI)	**72**	**76**			**Not estimable**
Total events: 0 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Clomiphene vs high purity urinary gonadotrophin					
Balasch 1994	0/38	0/40			Not estimable
Subtotal (95% CI)	**38**	**40**			**Not estimable**
Total events: 0 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Clomiphene vs recombinant FSH					
Nakajima 1999	0/27	0/28			Not estimable
Subtotal (95% CI)	**27**	**28**			**Not estimable**
Total events: 0 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**137**	**144**			**Not estimable**
Total events: 0 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

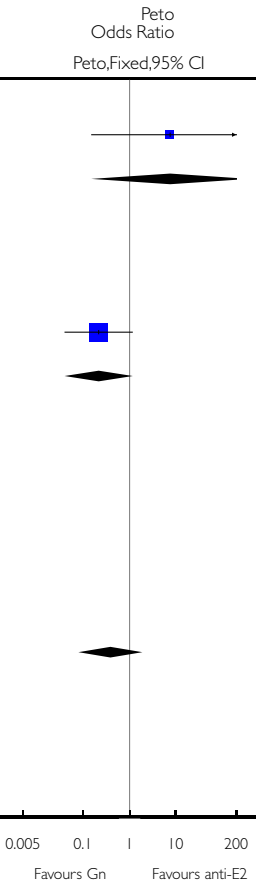
Analysis 2.1. Comparison 2 Anti-oestrogens vs gonadotrophins (excluding trials with hCG trigger co-intervention), Outcome 1 Pregnancy rate per woman.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 2 Anti-oestrogens vs gonadotrophins (excluding trials with hCG trigger co-intervention)

Outcome: 1 Pregnancy rate per woman

Study or subgroup	Anti-oestrogens n/N	Gonadotrophins n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Clomiphene vs human maternal gonadotrophins (hMG)					
Ecochard 2000	1/6	0/6		16.0 %	7.39 [0.15, 372.38]
Subtotal (95% CI)	**6**	**6**		**16.0 %**	**7.39 [0.15, 372.38]**
Total events: 1 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
2 Clomiphene vs high purity urinary gonadotrophin					
Balasch 1994	1/20	5/20		84.0 %	0.22 [0.04, 1.20]
Subtotal (95% CI)	**20**	**20**		**84.0 %**	**0.22 [0.04, 1.20]**
Total events: 1 (Anti-oestrogens), 5 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.080)					
3 Clomiphene vs recombinant FSH					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Anti-oestrogens), 0 (Gonadotrophins)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**26**	**26**		**100.0 %**	**0.38 [0.08, 1.84]**
Total events: 2 (Anti-oestrogens), 5 (Gonadotrophins)					
Heterogeneity: Chi^2 = 2.61, df = 1 (P = 0.11); I^2 =62%					
Test for overall effect: Z = 1.20 (P = 0.23)					
Test for subgroup differences: Chi^2 = 2.61, df = 1 (P = 0.11), I^2 =62%					

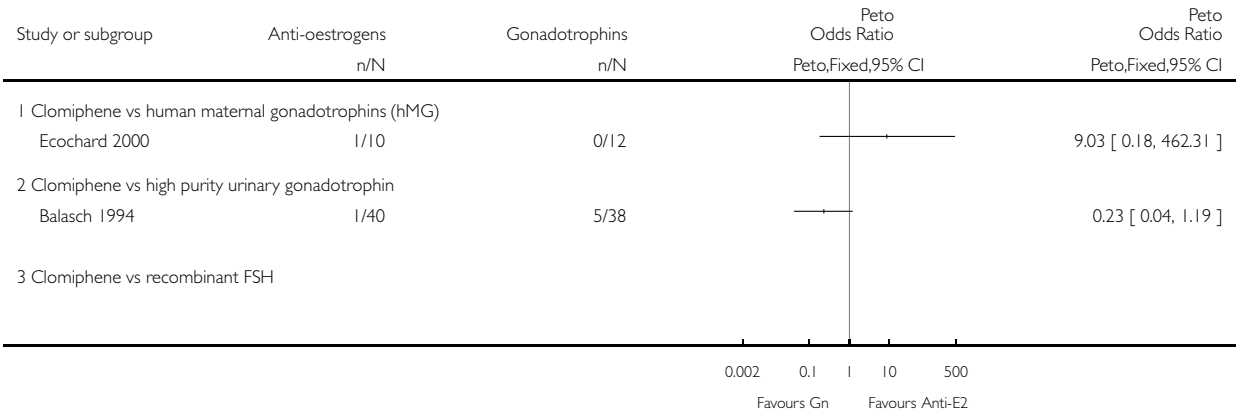


Analysis 2.2. Comparison 2 Anti-oestrogens vs gonadotrophins (excluding trials with hCG trigger co-intervention), Outcome 2 Pregnancy rate per cycle.

Review: Oral versus injectable ovulation induction agents for unexplained subfertility

Comparison: 2 Anti-oestrogens vs gonadotrophins (excluding trials with hCG trigger co-intervention)

Outcome: 2 Pregnancy rate per cycle



APPENDICES

Appendix 1. Search string

1. Clomiphene/
2 (clomiphene or Clomid).tw.
3 (clomiphene adj3 resist$).tw.
4 (1 or 2) not 3
5 exp fsh/ or exp gonadotropins, chorionic/ or exp lh/ or exp menotropins/
6 (FSH or "follicle stimulating hormone").tw.
7 (hmg or "human menopausal$").tw.
8 menotrop$.tw.
9 or/5-8
10 4 and 9
11 Breast neoplasms/ or "breast cancer".mp.
12 10 not 11
13 randomised controlled trial.pt.
14 controlled clinical trial.pt.
15 Randomized Controlled Trials/
16 Random allocation/
17 Double-blind method/
18 Single-Blind Method/
19 or/13-18

20 clinical trial.pt.
21 exp Clinical trials/
22 (clin$ adj25 trial$).ti,ab,sh.
23 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
24 Placebos/
25 placebo$.ti,ab,sh.
26 random$.ti,ab,sh.
27 Research design/
28 or/20-27
29 animal/ not (human/ and animal/)
30 19 or 28
31 30 not 29
32 12 and 31
33 Polycystic ovary syndrome/
34 32 not 33

WHAT'S NEW

Last assessed as up-to-date: 28 May 2002.

Date	Event	Description
12 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 3, 2002

Date	Event	Description
29 May 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Nat Athaullah: NA jointly with MP and NJ constructed the protocol. In particular he was involved in the background and methods section. Also he assessed the results described by the database searches and then analysed the reference section of the references.

Neil Johnson: NJ jointly with MP and NA constructed the protocol. He was the primary clinical input into the construction of the protocol.

Michelle Proctor: MP jointly with NJ and NA constructed the protocol. She also generated the search strings for the e-databases.

DECLARATIONS OF INTEREST

NJ works as a gynaecologist at Auckland City Hospital (a public hospital) in the National Women's Minimal Access Surgery and Endometriosis Service. NJ is also a private gynaecologist with groups called Endometriosis Auckland and IVF Auckland. Within the last 3 years NJ has received financial support to attend conferences or to arrange research meetings from the following companies: Organon, Serono, Schering and Device Technologies. NJ is an author of the Auckland LUNA Trial and of the Cochrane/systematic review on neuroablation and LUNA.

SOURCES OF SUPPORT

Internal sources

- University of Auckland, School of Medicine, Auckland, New Zealand.

External sources

- No sources of support supplied

NOTES

A new conflict of interest has been added

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Estrogen Antagonists [administration & dosage]; Fertility Agents, Female [*administration & dosage]; Gonadotropins [administration & dosage]; Infertility, Female [*drug therapy]; Ovulation Induction [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans