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Ovulation triggers in anovulatory women undergoing ovulation induction (Review)

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[Intervention Review]

Ovulation triggers in anovulatory women undergoing ovulation induction

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ABSTRACT

Background

Anovulation is a common cause of infertility. Drugs used to treat anovulation include selective oestrogen receptor modulators, aromatase inhibitors and gonadotrophins. Ovulation triggers are used with these drugs, as a surrogate for the hormonal surge seen in spontaneous menstrual cycles, to control the timing of ovulation and the timing of sexual intercourse. Ovulation triggers given without reliable evidence of oocyte maturity could be inappropriately timed; they increase costs, and the need to time intercourse precisely after the ovulation trigger is given adds to psychological stress.

This is an update of a Cochrane review first published in Issue 3, 2008, of the *Cochrane Database of Systematic Reviews.*

Objectives

To determine the benefits and harms of administering an ovulation trigger to anovulatory women receiving treatment with ovulation-inducing agents in comparison with spontaneous ovulation following ovulation induction.

Search methods

We updated searches of the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and PsycINFO to November 2013. We checked conference proceedings, trial registries and reference lists and contacted researchers.

Selection criteria

Parallel-group, randomised, controlled trials (RCTs) evaluating the administration of an ovulation trigger to anovulatory women receiving treatment with ovulation-inducing agents.

Data collection and analysis

We independently assessed trial eligibility and trial quality and extracted data. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data and used the random-effects model in meta-analyses when significant heterogeneity was present. We assessed overall quality of the evidence by using the GRADE approach.

Main results

No new trials were identified. This review includes two RCTs with low risk of bias that compared urinary human chorionic gonadotrophin (hCG) versus no treatment in anovulatory women receiving clomiphene citrate. Urinary hCG did not result in an increase in live birth rate over no hCG (OR 0.97, 95% CI 0.52 to 1.83; two trials, 305 participants, I^2 = 16%; *low-quality evidence*), but very serious imprecision around the effect estimate reduces our confidence in the apparent lack of effect of hCG as an ovulation trigger in clomiphene-induced cycles in anovulatory women.

Among this review's secondary outcomes, urinary hCG may not increase ovulation rate (OR 0.99, 95% CI 0.36 to 2.77; two trials, 305 participants, I^2 = 55%; *low-quality evidence*), clinical pregnancy rate (OR 1.02, 95% CI 0.56 to 1.89; two trials, 305 participants, I^2 = 35%; *low-quality evidence*) or miscarriage rate in pregnant women (OR 1.19, 95% CI 0.17 to 8.23; two trials, 54 participants, I^2 = 0%; *low-quality evidence*). Multiple pregnancies and preterm deliveries were uncommon, and ovarian hyperstimulation syndrome, adverse events and deaths were not reported as outcomes in either trial.

We found no trials evaluating other ovulation triggers.

Authors' conclusions

Evidence is inadequate to recommend or refute the use of urinary hCG as an ovulation trigger in anovulatory women treated with clomiphene citrate. We found no trials evaluating the use of ovulation triggers in anovulatory women treated with other ovulation-inducing agents.

PLAIN LANGUAGE SUMMARY

Use of medicines to help release eggs in women with infertility being treated with medicines to increase the growth of eggs

Review question

In women being treated with medicines to help eggs to grow (called ovulation induction), Cochrane authors wished to know whether adding medicines (called ovulation triggers) that help to release the egg (ovulation) would lead to more women having babies without causing harm compared with not giving them ovulation triggers. We found two randomised studies.

Background

Medicines that are given orally (e.g. clomiphene citrate) or by injection (e.g. gonadotrophins) are used to help eggs to grow in women who are unable to have children because they are not able to produce eggs (anovulation). In these women, instead of waiting for the eggs to be released spontaneously, additional medicines (called ovulation triggers) are often used (e.g. human chorionic gonadotrophin (hCG)) to help release the eggs. They are thought to improve the chances of ovulation occurring. They also help to control when ovulation occurs. This helps in timing more accurately when sexual intercourse should take place, so that the woman's chances of becoming pregnant are better. These ovulation triggers are given when the sac in which the egg is developing (follicle) is thought to be fully developed, based on ultrasound scans. However, this method is not always accurate and may lead to the ovulation trigger being given before the egg has matured. If eggs that are not fully developed are released, the chances of a successful pregnancy could be reduced. Couples are expected to have sex 36 hours after the ovulation trigger is given, and the need to stick to this timing may increase psychological stress for the couple. Ovulation triggers also add to the cost of treatment and occasionally may cause serious adverse events.

Study characteristics

The two studies included in this review randomly assigned 305 women being treated with clomiphene citrate to help eggs to develop to additionally receive a medicine (urinary hCG) to trigger their release or to receive no additional treatment. We found no trials comparing other ovulation triggers given with other medicines used for ovulation induction. The evidence is current to November 2013.

Key results

Giving women on clomiphene citrate additional urinary hCG may not increase their chances of delivering live babies, ovulating or becoming pregnant. Multiple pregnancies, miscarriages and preterm deliveries were not more common with or without an ovulation trigger. No serious adverse events were reported in either study.

Quality of the evidence

We cannot be certain whether ovulation triggers are better or worse than no ovulation triggers in women undergoing ovulation induction because not enough women were included in the two trials for definite results to be obtained. Larger trials in women undergoing ovulation induction that compare different ovulation triggers versus no additional treatment are needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

What are the effects of human chorionic gonadotrophin versus no ovulation trigger in clomiphene-induced cycles in women with anovulatory infertility?

Patient or population: women with anovulatory infertility undergoing ovulation induction with clomiphene citrate
Settings: infertility clinics in university hospitals
Intervention: human chorionic gonadotrophin (urinary hCG) versus no ovulation trigger in clomiphene-induced cycles

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No ovulation trigger	Human chorionic gonadotrophin				
Live birth rate Live fetus delivered beyond 20 completed weeks' gestation	**194 per 1000**	**189 per 1000** (111 to 306)	**OR 0.97** (0.52 to 1.83)	305 (two studies)	⊕⊕◯◯ **low**[1,2,3,4,5] (because of very serious imprecision)	
Ovulation rate Ultrasound evidence of collapsed follicle or mid-luteal serum progesterone <10 ng/mL	**861 per 1000**	**860 per 1000** (690 to 945)	**OR 0.99** (0.36 to 2.77)	305 (two studies)	⊕⊕◯◯ **low**[1,3,4,5,6] (because of very serious imprecision)	
Clinical pregnancy rate Ultrasound evidence of pregnancy	**200 per 1000**	**203 per 1000** (123 to 321)	**OR 1.02** (0.56 to 1.89)	305 (two studies)	⊕⊕◯◯ **low**[1,3,4,5,7] (because of very serious imprecision)	
Miscarriage rate per clinical pregnancy Spontaneous pregnancy loss before 20 weeks' gestation	**108 per 1000**	**126 per 1000** (20 to 499)	**OR 1.19** (0.17 to 8.23)	54 (two studies)	⊕⊕◯◯ **low**[1,3,4,5,8] (because of very serious imprecision)	

*The basis for the **assumed risk** is the median control group risk in the two studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No study limitations: Both trials were free of the risk of bias that could seriously undermine confidence in their results. Not downgraded.
[2]No serious Inconsistency: The trials differed in the direction of effect of the point estimates, but the confidence intervals overlapped, and I^2 was 16%. Not downgraded.
[3]No serious indirectness: Participants and interventions were representative of usual clinical practice. Not downgraded.
[4]Very serious imprecision: Upper and lower limits of the 95% CI indicated appreciable benefit for hCG and for no hCG, with no statistically significant difference; the total sample size in the two trials was much smaller than the optimal information size. Downgraded by two levels.
[5]Publication bias: It is unlikely that any study was missed.
[6]No serious inconsistency: Trials differed in direction of effect of point estimates, but confidence intervals overlapped, the Chi^2 test did not rule out chance (P value 0.14) and I^2 was 55%. Not downgraded.
[7]No serious inconsistency: Trials differed in direction of effect of point estimates, but confidence intervals overlapped, and I^2 was 35%. Not downgraded.
[8]No serious inconsistency: Trials differed in direction of effect of point estimates, but confidence intervals overlapped, and I^2 was 0%. Not downgraded.

BACKGROUND

Anovulation (absence of ovulation) and oligo-ovulation (infrequent or irregular ovulation) are common causes of infertility and constitute about 21% of the fertility problems in women (NICE 2004).

Description of the condition

Disorders of ovulation have been classified by the World Health Organization (WHO) into three groups (Speroff 2005a). Group 1 disorders are due to hypothalamic-pituitary failure, Group 2 disorders are due to hypothalamic-pituitary dysfunction, and Group 3 disorders are due to ovarian failure. Women in the WHO Group 2 usually present with oligomenorrhoea or amenorrhoea. They are not oestrogen deficient, they respond with a withdrawal bleed to progesterone challenge and they have normal gonadotrophin and prolactin levels. These disorders are common and include the polycystic ovarian syndrome (PCOS).

Pharmaceutical agents are used to induce ovulation. Orally effective drugs include selective oestrogen receptor modulators (SERMs) (like clomiphene citrate) and aromatase inhibitors. Gonadotrophins (injectables) generally are reserved for second-line therapy.

SERMs block oestrogen receptor sites in the hypothalamus and the pituitary, creating an impression of a low oestrogenic state. The higher centre of the brain responds with pulsatile release of gonadotrophin-releasing hormone (GnRH) and a consequent increase in follicle-stimulating hormone (FSH) and luteinising hormone (LH). This results in follicular growth and maturation (ASRM 2006). Clomiphene citrate remains the most commonly and extensively used anti-oestrogen. Tamoxifen, another anti-oestrogen, is used relatively infrequently for this indication.

Aromatase inhibitors have been used to induce ovulation in WHO Group 2 ovulatory dysfunction. They act at the level of the ovary to prevent the conversion of androgens to oestrogen by suppressing the enzyme aromatase. This releases the higher centres from the negative feedback of oestrogen, resulting in increased FSH production with subsequent follicular growth and maturation (Holzer 2006). Increased androgen levels in the ovary are also believed to increase sensitivity to FSH (Weil 1999). Absence of oestrogen receptor blockade makes this an attractive alternative to anti-estrogens, especially when the latter fail to elicit a response. Letrozole, anastrozole and exemestane are the commonly available compounds. Reports of an increased incidence of congenital malformations such as cardiac and locomotor abnormalities with the use of letrozole led to restrictions on the use of aromatase inhibitors (Biljan 2005). These abnormalities were not validated in a subsequent study, in which a larger number of babies were born following the use of letrozole (Tulandi 2006).

Gonadotrophins are indicated when oral preparations fail or are contraindicated because of side effects. These drugs stimulate follicular growth through direct action on the ovary (Macklon 2004). Gonadotrophin preparations are obtained from human menopausal urine or by recombinant technology. Depending on the purification process, urinary-derived gonadotrophins may be available as human menopausal gonadotrophin (hMG), purified FSH or highly purified FSH. The FSH content remains constant at 75 IU, and the LH content varies from 75 IU to 1 IU to 0.1 IU, respectively. In contrast, recombinant FSH (rFSH) contains 75 IU of FSH with no LH (Macklon 2004).

Although the aim of ovulation induction is mono-follicular development, caution needs to be exercised to prevent a hyperresponse. Development of several follicles, especially those seen in women with PCOS, can lead to multiple pregnancy and/or ovarian hyperstimulation syndrome (OHSS). OHSS is characterised by excessive ovarian response, leading to increased vascular permeability with resultant third space fluid accumulation (Barbieri 2004). Vaginal ultrasound is recommended to monitor follicular growth during ovulation induction, at least in the first treatment cycle, when oral agents are used, but it is considered mandatory when gonadotrophins are used (NICE 2004).

Description of the intervention

In a spontaneous menstrual cycle, the rising level of oestrogen produced from the developing follicle initiates an LH surge. This surge triggers the process of oocyte maturation and eventually results in its expulsion from the ovarian follicle. In anovulatory women, ovulation induction with SERMs, aromatase inhibitors or gonadotrophins initiates and sustains follicular development. Ovulation triggers are advocated as a surrogate for the endogenous LH surge to achieve better control of the timing of ovulation. In ovulation induction cycles monitored by ultrasound, ovulation triggers are administered once follicular size has reached 18 to 22 mm.

How the intervention might work

In artificially induced and normal ovulation cycles, the precise timing of ovulation is unclear, and follicular size acts as a marker of oocyte development. Follicles that have reached a size of 18 mm on ultrasound are presumed to contain mature oocytes. Without ovulation triggers, follicular size is used to infer that ovulation is likely to occur, and intercourse is encouraged. Administration of an ovulation trigger permits better control over the timing of the LH surge and the reliability of occurrence of ovulation; it also provides the opportunity for better timing of intercourse or intrauterine insemination.

Urinary-derived human hCG is commonly used to trigger ovulation. Available alternative drugs include recombinant hCG (rhCG), recombinant LH (rLH) and a gonadotrophin-releasing hormone (GnRH) agonist. The hCG (urinary or recombinant)

and the rLH act directly on the follicle, while GnRH agonists stimulate the release of endogenous LH from the pituitary (Macklon 2004).

Why it is important to do this review

Administration of an ovulation trigger depends entirely upon ultrasound measurement of follicular size and does not take into account the actual process of oocyte development. As follicular size is only an indirect marker of oocyte maturity, the ovulation trigger could be mis-timed, with the consequent LH surge resulting in the release of developmentally compromised oocytes. Premature administration may, therefore, affect oocyte quality, thereby negatively influencing the pregnancy rate. Rarely, luteinised unruptured follicles may also occur (Coetsier 1996). In addition to the fact that they are expensive, administration of ovulation triggers and timing of sexual intercourse to occur 36 hours later to maximise the chances of conception add to psychological stress for the couple. Ovarian hyperstimulation syndrome (which can be fatal) is more common when hCG is used to induce ovulation (Delvigne 2002).

Spontaneous ovulation is a natural process that perhaps allows better oocyte maturation and quality; this could result in a physiologically normal corpus luteum, a normal luteal phase and possibly better pregnancy rates. The practise of administering an ovulation trigger has not been rigorously tested, and questions remain regarding the efficacy of its use in comparison with spontaneous ovulation in women receiving ovulation induction agents for the treatment of anovulatory infertility.

This is an update of a Cochrane review (George 2008). In our previous search, we had identified two relevant trials evaluating urinary hCG versus no ovulation trigger in anovulatory women undergoing ovulation induction with clomiphene citrate, but no conclusions could be drawn on the role of ovulation triggers because the data were inconclusive. In this updated review, we updated the search done in 2007 and incorporated advances in methods in accordance with the methodological requirements of Cochrane intervention reviews (MECIR 2011).

OBJECTIVES

To determine the benefits and harms of administering an ovulation trigger to anovulatory women receiving treatment with ovulation-inducing agents in comparison with spontaneous ovulation following ovulation induction.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel-group, randomised, controlled trials evaluating the administration of an ovulation trigger to anovulatory women receiving treatment with ovulation-inducing agents. Cross-over trials and quasi-randomised trials were excluded.

Types of participants

Women with anovulatory infertility diagnosed by:

- Irregular cycles-shorter than 21 days or longer than 35 days;
- Mid-luteal serum progesterone < 10 ng/mL (Speroff 2005b); or
- Both.

and undergoing ovulation induction using SERMs (clomiphene citrate or tamoxifen), gonadotrophins (hMG, purified FSH, highly purified FSH or recombinant FSH) or aromatase inhibitors (letrozole, anastrozole or exemestane).

Types of interventions

Interventions

- Urinary hCG.
- Recombinant hCG (rhCG).
- Recombinant LH (rLH).
- GnRH agonists.

Control

- Placebo or no treatment.

Types of outcome measures

Primary outcomes

- Live birth rate: birth in which a fetus is delivered with signs of life after complete expulsion or extraction from its mother, beyond 20 completed weeks' gestational age (ICMART 2006).

Secondary outcomes

- Ovulation rate per woman: diagnosed by ultrasound evidence of collapse of a follicle, serum progesterone measured in the mid-luteal phase greater than 10 ng/mL (ASRM 2006) or both.
- Clinical pregnancy rate: determined by ultrasound evidence of pregnancy, including ectopic pregnancy; multiple gestations were counted as one (ICMART 2006).
- Multiple pregnancy rate: determined by the presence of more than one gestational sac detected by ultrasound at six to eight weeks' gestation.

- Miscarriage rate: measured as spontaneous pregnancy loss before 20 weeks' gestation.
- Preterm delivery rate: identified as spontaneous delivery at less than 37 weeks' gestation.
- Ovarian hyperstimulation syndrome: diagnosed by symptoms and signs, including use of ultrasound.
- Adverse events: local and systemic.
- Mortality.

Search methods for identification of studies

Electronic searches

Databases

Marian Showell, the Trial Search Co-ordinator of the Menstrual Disorders and Subfertility Group (MDSG), updated searches of the MDSG Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 11), MEDLINE, EMBASE and PsycINFO from August 2007 to 14 November 2013, using the keywords described in the appendices. The Menstrual Disorders and Subfertility Database search string used is described in Appendix 1. The search strategies used for CENTRAL (Appendix 2), MEDLINE (Appendix 3), EMBASE (Appendix 4) and PsycINFO (Appendix 5) are also described. Search terms were combined with the Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE (sensitivity-maximising version, 2008 revision) in the Ovid format (Higgins 2011). No restrictions were applied for language or publication status.

Conference proceedings

We handsearched conference abstracts and announcements from the American Society for Reproductive Medicine (ASRM) (2008 to 2013) (www.asrm.org/annualmeeting.aspx), the European Society of Human Reproduction and Embryology (ESHRE) (2008 to 2013) (www.eshre.eu/annual_meeting/page.aspx/11) and the World Congress on Infertility and Sterility (IFFS Congress) (2008 to 2013) (www.iffs-reproduction.org/congress.htm).

Clinical trial registries

We also searched the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/mrct/), the US National Institutes of Health trials registry (www.clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/) for ongoing and completed but unpublished trials.

Searching other resources

Reference lists

We checked the reference lists of all studies identified by the above methods.

Researchers

We contacted the authors of trials identified by our search to ask for information regarding additional trials.

Data collection and analysis

Selection of studies

Three review authors (KG, MSK and RN) independently inspected the citations identified by the search. Potentially relevant abstracts were identified and full papers obtained and assessed for inclusion in accordance with the defined criteria. Disagreement during this process was resolved by discussion with the fourth review author (PT) and by contacting the trial authors to ask for clarification.

Data extraction and management

We independently extracted data from the trials using a predesigned data extraction form. We contacted the authors of trials with insufficient or missing data to ask for more information. Disagreements, if any, were resolved by referring to the trial report and through discussion. Two review authors (MSK and RN) entered the data into Review Manager 5.2, and this information was independently checked by the other two review authors (KG and PT).

For the dichotomous outcome measures used in this review, we recorded the number of participants experiencing the event and the number analysed in each group.

Assessment of risk of bias in included studies

We independently assessed the risk of bias in each included study. Disagreements, if any, were resolved by referring to the trial report, by corresponding with the authors of the report and through discussion. We assessed each study on the domains of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective reporting; and other sources of bias. For each of these components, we assigned a judgement regarding the risk of bias as 'high', 'low' or 'unclear', using criteria laid down in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We recorded these assessments in the standard 'Risk of bias' tables in Review

Manager 5.2 and summarised the risk of bias for each study in a summary risk of bias figure and graph.

Measures of treatment effect

We compared dichotomous outcomes using odds ratios (ORs) and presented all results along with their 95% confidence intervals (CIs).

Unit of analysis issues

The primary analysis was per woman randomly assigned.

Dealing with missing data

We conducted intention-to-treat analysis in trials with no loss to follow-up and completed-case analysis for trials with incomplete follow-up. We attempted to obtain missing data from study authors. We made no assumptions about those lost to follow-up but utilised this information in assessing each study for risk of attrition bias due to incomplete outcome data reporting, and in assessing the overall quality of evidence for each outcome in the summary of findings tables for each comparison.

Assessment of heterogeneity

After considering the likelihood of clinical heterogeneity based on comparison of the included studies, we visually inspected graphs to investigate the possibility of statistical heterogeneity and used a P value less than 0.1 for the Chi^2 test for homogeneity to indicate significant heterogeneity. We used the I^2 statistic to provide an estimate of the percentage of variability due to heterogeneity, in excess of chance. We interpreted an I^2 value of 50% or greater as indicating a moderate level of heterogeneity (Higgins 2003), used the random-effects model and recommended cautious interpretation of the results.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we attempted to minimise their potential impact by ensuring a comprehensive search for eligible studies and by staying alert for duplication of data. Had at least 10 trials been identified for analysis, we planned to use funnel plots to explore the possibility of small-study effects (the tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We synthesised data using Review Manager 5.2, and we used the Mantel-Haenszel method to derive pooled, weighted ORs and CIs in fixed-effect meta-analyses. When heterogeneity was significant ($I^2 \geq 50\%$), we combined the results of trials using a random-effects model if the trials were clinically sufficiently similar to allow pooling, and if the resulting estimate was still interpretable. If severe heterogeneity was detected ($I^2 \geq 75\%$) that could not be explained by differences across trials in terms of clinical or methodological features or by subgroup analyses (see later), we planned to present the results of individual trials in a forest plot, without pooling of results.

Subgroup analysis and investigation of heterogeneity

We planned to subgroup trials, if possible, to investigate heterogeneity according to the dose of hCG used (5000 IU or 10,000 IU) and obesity (defined as body mass index (BMI) > 30 kg/m^2).

Sensitivity analysis

The planned sensitivity analysis would have excluded studies with more than 20% attrition. However, this was not required, as attrition in the two trials was low.

Summarising and interpreting results

We used the GRADE approach to interpret findings (Schunemann 2008). We used GRADE Profiler software (GRADE 2004) and imported data from Review Manager 5.2 to create 'Summary of findings' tables for each comparison included in this review. These tables provide information concerning the overall quality of evidence derived from the trials, the magnitude of effect of the interventions examined and the sum of available data on the primary outcome and on secondary outcomes rated as important or critically important to health decision making.
Outcomes selected for inclusion in these tables were:

- Live birth rate;
- Ovulation rate;
- Clinical pregnancy rate; and
- Miscarriage rate.

These summary of findings tables were used to guide our conclusions and recommendations.

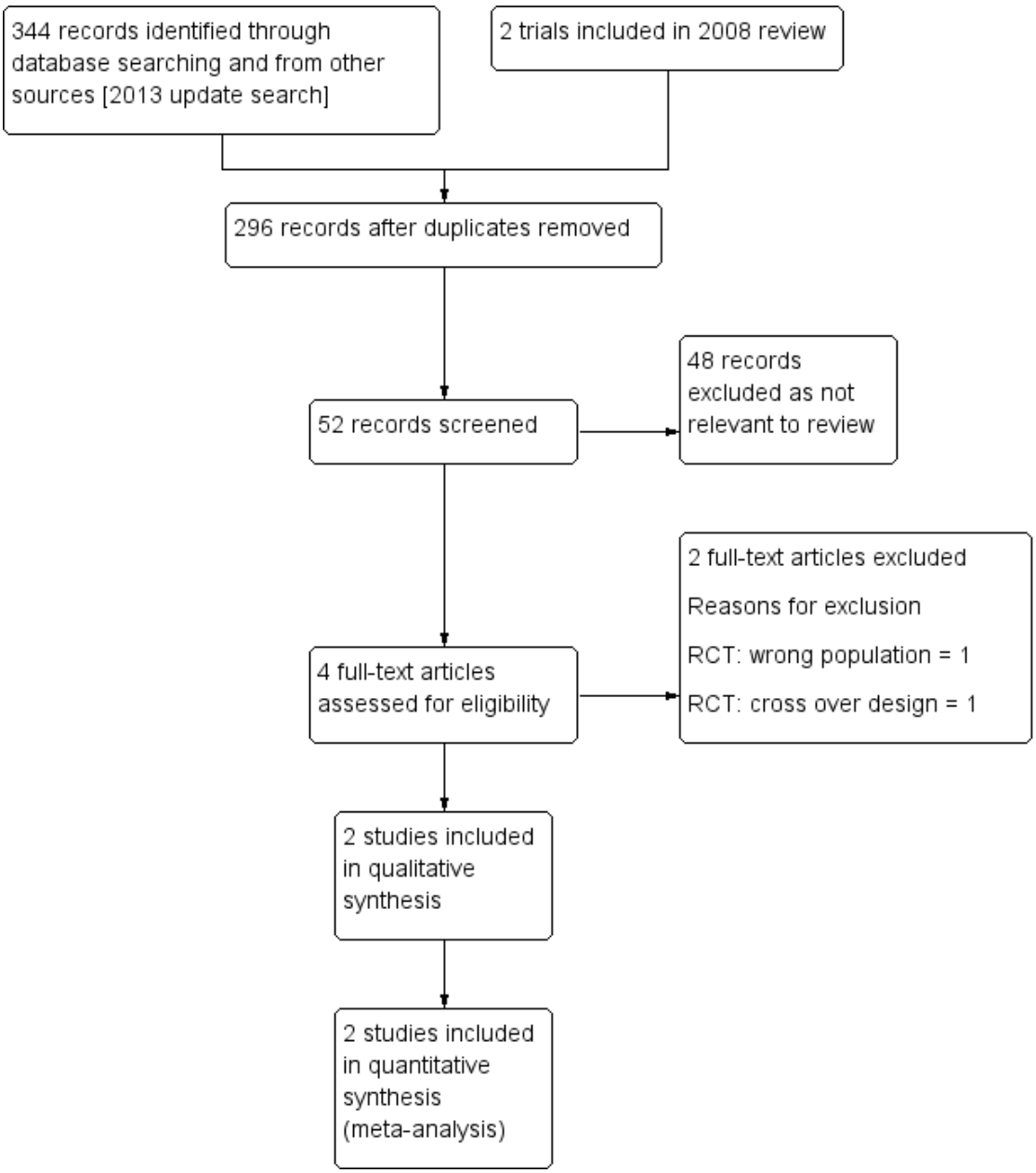
RESULTS

Description of studies

Results of the search

Our search in 2007 yielded four potentially eligible studies in which urinary hCG was used as an ovulatory trigger in women treated for anovulation with clomiphene citrate, of which two trials were included in the initial review (George 2008). The 2013 search update revealed no new trials that fulfilled inclusion criteria for this review. See Figure 1 for details of the selection process.

Figure 1. Study flow diagram.



Our search identified no studies evaluating recombinant hCG, recombinant LH or GnRH agonists as ovulation triggers in anovulatory women undergoing ovulation induction using SERMs (clomiphene citrate/tamoxifen), aromatase inhibitors (letrozole, anastrozole or exemestane) or gonadotrophins (hMG, purified

FSH, highly purified FSH or recombinant FSH).

We are not aware of any ongoing studies. No studies currently await assessment.

Included studies

Study design and setting

Both of the included studies were parallel-design, randomised, controlled trials. George 2007 was conducted in a single centre in India, and Yilmaz 2006 was conducted in two centres in Turkey. These studies are described in detail in the Characteristics of included studies.

Participants

The two included studies (George 2007; Yilmaz 2006) enrolled a total of 305 women (urinary hCG trigger group = 150; no trigger group = 155). In both trials, anovulatory women receiving treatment with clomiphene citrate were included. Anovulation was diagnosed on the basis of oligomenorrhoea, secondary amenorrhoea or serum progesterone assessed in the mid-luteal phase. In both trials, baseline demographic characteristics such as age, BMI, follicular size and number were similar between the two groups.

Interventions

In both trials, anovulatory women treated with clomiphene citrate were randomly assigned to receive urinary hCG as an ovulatory trigger or to a no treatment arm; women assigned to the latter arm awaited a spontaneous LH surge.

In Yilmaz 2006, a full infertility workup including tubal evaluation was done; in George 2007, only a basic infertility workup was carried out, after which treatment for anovulation was initiated. In Yilmaz 2006, recruited women were randomly assigned before treatment, hence some women (n = 23) did not respond to treatment. In George 2007, women undergoing treatment were randomly assigned after a dominant follicle was determined by ultrasound scan, hence no treatment failures were reported.

Outcomes

Data were extracted from trial reports or were provided by study authors for the following outcomes.

- Ovulation rates.
- Clinical pregnancy rates.
- Miscarriage rates.
- Preterm labour rates.
- Live birth rates.

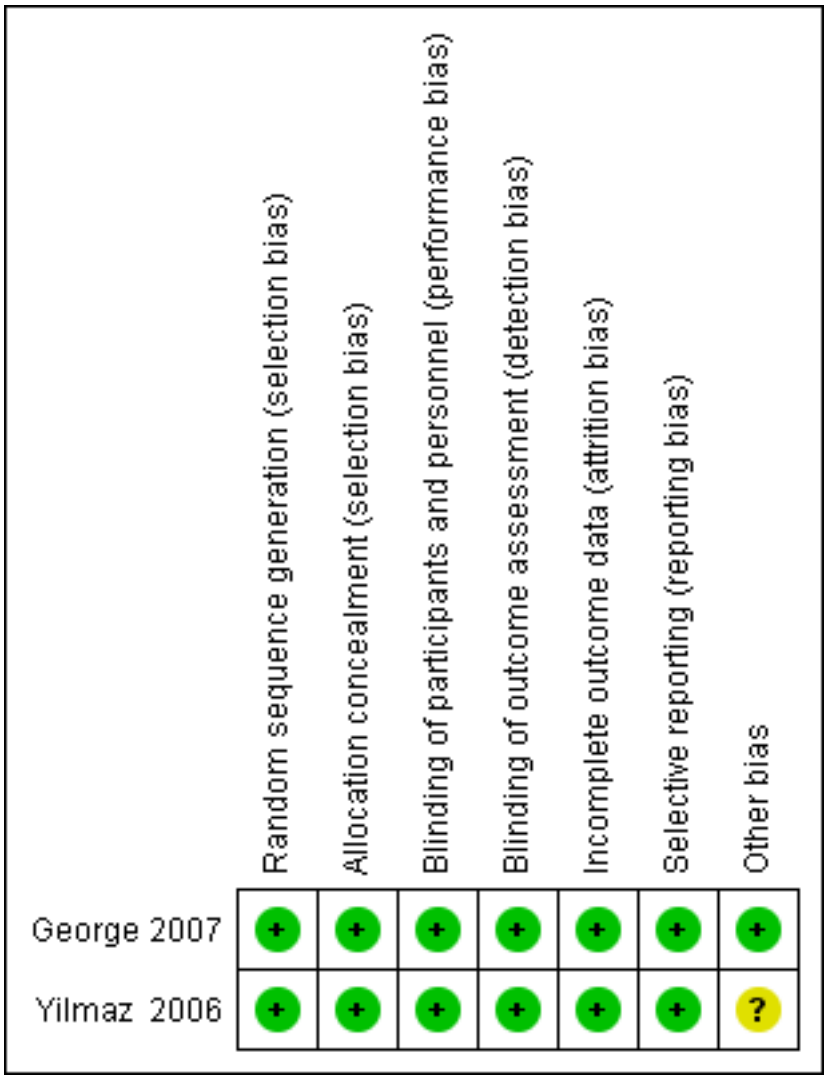
Excluded studies

Two potentially eligible studies (Harrison 1983; Sutaria 1980) were excluded, as they did not meet our inclusion criteria; the reasons for exclusion are provided in Characteristics of excluded studies.

Risk of bias in included studies

See 'Risk of bias' tables for the two included trials in Characteristics of included studies and in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Both trials were judged to be at low risk of selection bias because they used random number tables to generate the randomisation sequence and concealed allocation by using opaque envelopes that contained the randomised allocation.

Blinding

Yilmaz 2006 blinded sonographers who evaluated follicular size. Neither participants nor other investigators were reported to have been blinded to interventions. George 2007 was an open trial. In both trials, even though participants and the investigator were not blinded, the risk of performance bias was judged to be low. Even though both trials were open-label, the outcomes were objective. The risk of detection bias was considered to be low.

Incomplete outcome data

The attrition rate was low in both trials (Yilmaz 2006: 6%; George 2007: < 2%).

Selective reporting

Both studies were not prospectively registered. However, both reported in their results outcomes stated in the methods section, hence the risk of reporting bias was judged to be low.

Other potential sources of bias

In Yilmaz 2006, the number of participants recruited did not reach the calculated sample size, and no clear explanation was given for premature stopping of the trial. Twenty-three participants did not respond (no follicular development) after randomisation. The differential attrition rates in the two arms of the trial were roughly similar. It was unclear whether eight of the 133 participants were lost to follow-up before or after randomisation, and their allocation was not reported. The source of funding was not reported. This trial was judged as unclear for the risk of other sources of bias because of these factors.
In George 2007, no other sources of bias were detected.

Effects of interventions

See: **Summary of findings for the main comparison** Human chorionic gonadotrophin versus no ovulation trigger in clomiphene-induced cycles

Urinary hCG versus no treatment in anovulatory women treated with clomiphene citrate

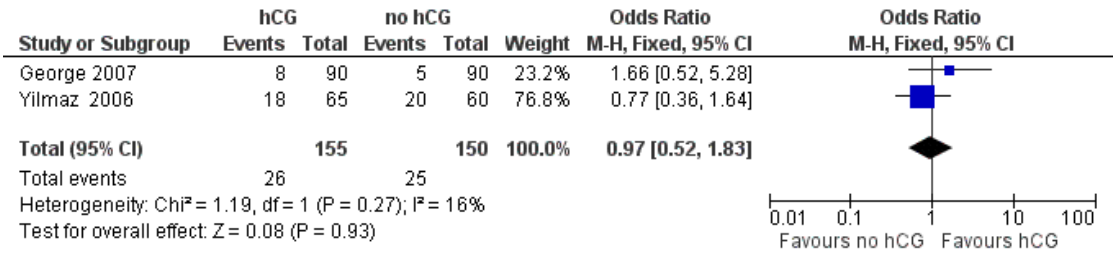
Data from the two included trials (George 2007; Yilmaz 2006) were pooled and addressed the primary and secondary outcomes of this review. See Summary of findings for the main comparison.

Primary outcome

Live birth rate

Live births in randomly assigned women did not differ significantly with urinary hCG or no hCG after ovulation induction with clomiphene citrate (OR 0.97, 95% CI 0.52 to 1.83; two trials, 305 participants, I^2 = 16%; Figure 3; Analysis 1.1).

Figure 3. Forest plot of comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), outcome: 1.1 Live birth rate per woman randomly assigned.

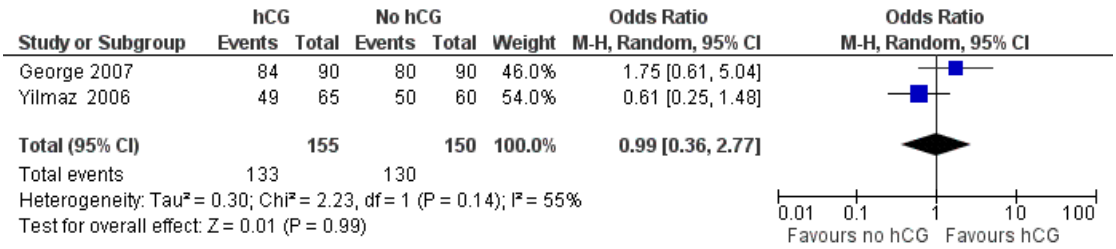


Secondary outcomes

Ovulation rate

Ovulation rate in randomly assigned women did not differ significantly with urinary hCG or no hCG (OR 0.99, 95% CI 0.36 to 2.77; two trials, 305 participants, I^2 = 55%; Figure 4 Analysis 1.2). Pooled data from both trials revealed a moderate degree of intertrial variability, with effect estimates that differed in the direction of effect (I^2 = 55%), hence the random-effects model was used for meta-analysis.

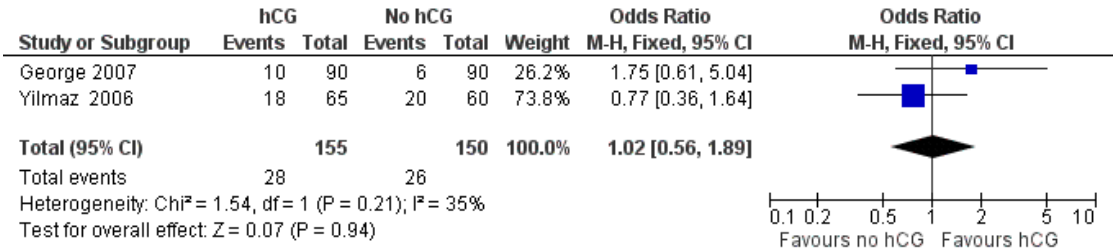
Figure 4. Forest plot of comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), outcome: 1.2 Ovulation rate per woman randomly assigned.



Clinical pregnancy rate

Clinical pregnancy rate per woman randomly assigned did not significantly differ with urinary hCG or no hCG (OR 1.02, 95% CI 0.56 to 1.89; two trials, 305 participants, I^2 = 35%; Figure 5; Analysis 1.3).

Figure 5. Forest plot of comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), outcome: 1.3 Clinical pregnancy rate per woman randomly assigned.



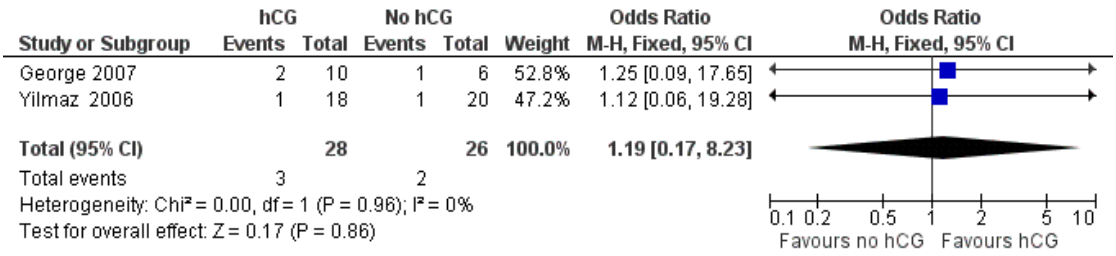
Multiple pregnancy rate

George 2007 did not report multiple pregnancies in either intervention arm. The multiple pregnancy rate per woman randomly assigned in Yilmaz 2006 did not differ significantly with urinary hCG or no hCG (OR 0.45, 95% CI 0.04 to 5.13; two trials, 305 participants; Analysis 1.4).

Miscarriage rate

The number of miscarriages per clinical pregnancy did not significantly differ between urinary hCG and no hCG arms (OR 1.19, 95% CI 0.17 to 8.23; I^2 = 0%, two trials, 54 participants; Figure 6; Analysis 1.5).

Figure 6. Forest plot of comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), outcome: 1.5 Miscarriage rate per clinical pregnancy.



Preterm delivery rate

Only one preterm delivery was reported in Yilmaz 2006; it occurred in the no treatment arm (Analysis 1.6).

Ovarian hyperstimulation syndrome

This outcome was not reported in either trial.

Adverse events

Adverse events were not reported in either trial.

Mortality

No deaths were reported to have occurred in the two trials.

Subgroup analyses

In George 2007, the hCG dose used was 5000 IU, and Yilmaz 2006 used 10,000 IU. Because both trials did not reveal significant differences between intervention arms for all outcomes reviewed, subgroup analysis for the dose of hCG was not indicated. Subgroup analysis based on BMI was not possible.

Sensitivity analyses

The attrition rate was low in both trials, hence the planned sensitivity analysis was not indicated.

No studies evaluated recombinant hCG, recombinant LH or GnRH agonists as ovulation triggers in anovulatory women undergoing ovulation induction using SERMs (clomiphene citrate/tamoxifen), aromatase inhibitors (letrozole, anastrozole or exemestane) or gonadotrophins (hMG, purified FSH, highly purified FSH or recombinant FSH).

DISCUSSION

Summary of main results

We identified only two RCTs addressing the objectives of this review. These trials compared urinary hCG versus no ovulation trigger in anovulatory women undergoing ovulation induction with clomiphene citrate.

Ovulation induction with or without urinary hCG as an ovulation trigger may be similar with regard to live birth rate, ovulation rate, clinical pregnancy rate, multiple pregnancy rate or miscarriage rate per clinical pregnancy, but we cannot be certain that ovulation triggers do not confer any advantage over no treatment because the combined sample size in the two trials was underpowered to rule out a clinically important benefit with urinary hCG (see Summary of findings for the main comparison). Both trials were powered to detect only differences in ovulation rates, and one study (Yilmaz 2006) did not achieve the recruitment target. Preterm deliveries were uncommon, and ovarian hyperstimulation syndrome, adverse events and deaths were not reported in either trial.

Overall completeness and applicability of evidence

Completeness

We believe that our search was thorough, yet we did not identify any studies evaluating recombinant hCG, recombinant LH or GnRH agonists as ovulation triggers in anovulatory women undergoing ovulation induction using SERMs (clomiphene citrate/tamoxifen), aromatase inhibitors (letrozole, anastrozole or exemestane) or gonadotrophins (hMG, purified FSH, highly purified FSH or recombinant FSH). Our search revealed a plethora of trials comparing different ovulation triggers, but unfortunately, there is a paucity of trials evaluating each ovulation trigger versus no treatment or placebo.

Applicability

No evidence of a clinically beneficial effect of urinary hCG was seen compared with no ovulation trigger in women undergoing ovulation induction with clomiphene. This does not necessarily mean that urinary hCG has no beneficial effect.

Clinical pregnancy rates were higher in Yilmaz 2006 (28%), which used 10,000 IU of urinary hCG, compared with George 2007 (11%), which used a lower dose of urinary hCG (5000 IU). One could speculate that the higher dose in Yilmaz 2006 would therefore be preferable. However, the no treatment arm in Yilmaz 2006 revealed an equally high clinical pregnancy rate (33.33%), suggesting the need for more robust evidence before the optimal dose of urinary hCG can be determined. Although 5000 IU is considered the standard minimum dose, wide variability has been noted in the doses used, with little evidence to support any particular dose (Nargund 2007). Although not observed in Yilmaz 2006, use of the higher dose could lead to development of OHSS in high-dose responders.

Quality of the evidence

Assessments of overall quality of evidence were made using the GRADE approach (Schunemann 2008). The GRADE approach considers 'quality' to be a judgement of the extent to which one can be confident that the estimates of effect are correct. 'Quality' is graded for each outcome on five domains. Evidence from randomised controlled studies is initially graded as high and is downgraded by one or two levels on each domain after full consideration of any limitations in the design of studies, the directness (or applicability) of evidence, the consistency and precision of results and the possibility of publication bias. This results in assessment of the quality of a body of evidence as*high, moderate, low* or*very low*. A GRADE quality level of *high* reflects confidence that the true effect lies close to that of the estimate of effect for an outcome. A judgement of *moderate* quality indicates that the true effect is likely to be close to the estimate of effect but acknowledges the possibility that it is substantially different. *Low* or *very low* quality of evidence limits our confidence in the effect estimate (Balshem 2011).

These judgements for preselected patient-important outcomes for each comparison in this review are presented in Summary of findings for the main comparison. The overall quality of evidence for all preselected outcomes was graded as *low* because of very serious imprecision, possibly due to inadequate sample size, that did not rule out the effects of random error.

Potential biases in the review process

We used standard methods described in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and complied with the methodological standards of The Cochrane Collaboration for the conduct of intervention reviews (MECIR 2011).

One of the included trials was conducted by two of the authors of this review-KG and RN (George 2007). The other two review authors-MSK and PT-were involved in evaluating the risk of bias for both included studies and provided independent evaluations of any potential biases in interpretation of evidence from both trials.

Agreements and disagreements with other studies or reviews

No reviews were identified that addressed the review question.

AUTHORS' CONCLUSIONS

Implications for practice

This updated systematic review does not provide conclusive evidence to recommend or refute the use of urinary hCG, as an ovulation trigger, in anovulatory women treated with clomiphene citrate.

Limited data from this review provide no evidence to suggest that urinary hCG used as an ovulatory trigger in anovulatory women receiving clomiphene citrate improves the outcomes of live birth, ovulation, clinical pregnancy, miscarriage, multiple pregnancy and preterm delivery compared with not using an ovulatory trigger, but limited data from the two included trials do not provide conclusive evidence to refute its use.

The use of other ovulation triggers in anovulatory women treated with other ovulation-inducing agents has not been properly evaluated.

Implications for research

The role of ovulation-inducing agents in anovulatory women is well established (Brown 2009). Although various ovulation triggers are commonly used in clinical practice, evidence is insufficient to support this role.

Since the time of publication of the initial version of this review (George 2008), no trials on the need for ovulation triggers in anovulatory women undergoing treatment have been published. In spite of lack of evidence, the current focus appears to be on the comparison of different types of ovulation triggers through many published reports. The question "Is a trigger necessary or beneficial?" needs to be addressed first.

More trials that are adequately powered and that directly compare different ovulation triggers versus placebo/no treatment are required before recommendations can be made. A larger study is also needed to evaluate the efficacy of urinary hCG as an ovulation trigger in anovulatory women. Any future study evaluating the role of urinary hCG in anovulatory women treated with clomiphene

citrate needs to take into account the following: The live birth rate with the use of clomiphene citrate has not been reported in randomised trials but is likely to be in the range of 30% (Homburg 2005). To estimate a 5% difference in live birth rates with the use of urinary hCG, a sample size of 2800 women will be required. This would best be addressed in the form of a well-planned multicentre study.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

George 2007

Methods	**Method:** randomised, single-centre, parallel-group, open-label, controlled trial **Trial duration:** one year
Participants	**Number randomly assigned:** 180 **Inclusion criteria** • Anovulatory women planned for ovulation induction with clomiphene citrate • Anovulation diagnosed by irregular cycles of longer than 35 days or by serum progesterone > 10 ng/mL carried out on the 21st day of the cycle in women with regular 28-day cycles Baseline characteristics included age, BMI, dose of drugs used, number and size of dominant follicle, ovulation monitored by ultrasound and serum progesterone
Interventions	**Intervention** hCG 5000 IU intramuscularly in the morning between 9 AM and 10 AM; couples were advised to have intercourse the following night, about 36 hours later (n = 90) **Control** No hCG trigger; participants were advised to have intercourse frequently over the next few days (n = 90) In both arms, clomiphene citrate was started from day two at a starting dose of 100 mg daily, monitored by transvaginal ultrasound on day 13 and afterwards, depending upon follicular size and growth Follicle judged to be mature when measuring 18 mm or larger Randomisation to respective groups was carried out after follicular development Ovulation was assessed by ultrasound after four days and by serum progesterone after seven days
Outcomes	**Outcomes included in review** • Ovulation by ultrasound/serum progesterone • Clinical pregnancy rates • Miscarriage rates • Live birth rate **Additional outcome in the trial not included in the review** • Biochemical pregnancy rate **Additional outcomes provided by the author and included in the review but not reported in the trial publication** • Multiple pregnancy rate • Preterm delivery rate
Notes	**Setting:** Reproductive Medicine Unit, Department of Obstetrics and Gynaecology, Christian Medical College & Hospital, Vellore, Tamil Nadu, India **Funding:** intramural research funds of the Christian Medical College, Vellore **Comments** • Sample size calculated as 90 women in each arm, based on anticipated ovulation rate

George 2007 (*Continued*)

	• Randomisation was done once the dominant follicle was observed on ultrasound

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from report: "random numbers were generated using randomisation tables"
Allocation concealment (selection bias)	Low risk	Quote from report: by "opening consecutively numbered sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label trial. Even though participants and the investigator were not blinded, risk of performance bias was considered unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label trial. However, all outcomes were objective; possibility of detection bias unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very low attrition rate (< 2%). Quote from report arm: "One woman in group A (hCG) and 2 women in group B (no hCG) were lost to follow-up after randomisation and were not evaluated in the trial"
Selective reporting (reporting bias)	Low risk	Even though the trial protocol was not available, all prestated outcomes were reported
Other bias	Low risk	No other bias detected

Yilmaz 2006

Methods	**Method:** Randomised, two-centre, parallel-group, single-blinded, controlled trial **Trial duration:** two years (from May 2002 to April 2004)
Participants	**Number randomly assigned:** 133 **Inclusion criteria** • Primary infertility • Normoprolactinemic and normogonadotropic (WHO class 2 ovarian dysfunction) • Age 20 to 40 years • Duration of primary infertility: two years • No history of ovulation induction treatment and thyroid disease • Normal results on hysterosalpingogram • Normal semen analysis

	Anovulation diagnosed by oligomenorrhoea (35 days to six months)/amenorrhoea longer than six months Baseline characteristics include age, BMI, duration of infertility, type of infertility, semen analysis report, dose of drugs used, number and size of dominant follicles, ovulation by ultrasound and serum progesterone
Interventions	**Intervention** hCG 10,000 units (Pregnyl 10,000 IU IM) was administered when one or more follicles reached 18 mm diameter by ultrasound. Intercourse was advised accordingly (n = 60) **Control** No hCG; natural intercourse advised five days after last dose of clomiphene citrate (n = 65) In both arms, clomiphene citrate 50 mg was given from day five to day nine Ovulation was assessed by ultrasound and by serum progesterone level
Outcomes	**Outcomes included in review** • Ovulation rate • Pregnancy rate • Clinical pregnancy rate • Multiple pregnancy rate • Preterm delivery rate **Outcomes reported in the trial and not included in the review** • Fertilisation rate • Implantation rate • Abortion rate • Assessment of luteal phase by mid-luteal serum progesterone • Luteal phase length. **Outcome provided by the author and included in the review but not reported in the trial publication** • Live birth rate • Preterm delivery rate • Miscarriage rate
Notes	**Setting:** Department of Reproductive Endocrinology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara; and Department of Reproductive Endocrinology, Suleymaniye Maternity Hospital, Istanbul, Turkey **Funding:** not mentioned **Comments** • Sample size calculated was 117 in each arm, based on anticipated ovulation rate. Of 133 women (unclear whether eligible or randomised), eight were lost to follow-up, and results were reported for 125 randomly assigned women. Reason for not achieving calculated sample size not mentioned • Randomisation done before the start of therapy. Twenty-three women did not respond to ovulation induction • Definition of abortion: detected chemically but not by ultrasound scan at seven weeks' gestation • Analysis was by intention-to-treat
Risk of bias	

Yilmaz 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the report: "determined by a random number table"
Allocation concealment (selection bias)	Low risk	Quote from the report: "opaque envelope technique"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The sonographer was blinded. Even though participants and other investigators were not blinded, the risk of performance bias is highly unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes were objective; possibility of detection bias unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eight participants among the 133 women dropped out of the study, and their allocated intervention was unclear. All other randomly assigned participants completed the study. The numbers completing the trial in both arms were roughly similar and would not alter the results significantly
Selective reporting (reporting bias)	Low risk	Even though the trial protocol was not available, all prestated outcomes were reported
Other bias	Unclear risk	The number of women recruited did not reach the calculated sample size (117 in each arm). Reason for not achieving calculated sample size not mentioned Twenty-three women did not respond (did not develop a follicle) after randomisation. However, the numbers completing the trial were roughly equal in the two arms

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

Study	Reason for exclusion
Harrison 1983	RCT; women with unexplained infertility were studied
Sutaria 1980	RCT: cross-over design

DATA AND ANALYSES

Comparison 1. Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman randomly assigned	2	305	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.52, 1.83]
2 Ovulation rate per woman randomly assigned	2	305	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.36, 2.77]
3 Clinical pregnancy rate per woman randomly assigned	2	305	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.56, 1.89]
4 Multiple pregnancy rate per woman randomly assigned	2	305	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.04, 5.13]
5 Miscarriage rate per clinical pregnancy	2	54	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.17, 8.23]
6 Preterm delivery rate per woman randomly assigned	2	305	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 7.58]

Analysis 1.1. Comparison 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), Outcome 1 Live birth rate per woman randomly assigned.

Review: Ovulation triggers in anovulatory women undergoing ovulation induction

Comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles)

Outcome: 1 Live birth rate per woman randomly assigned

Study or subgroup	hCG n/N	no hCG n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
George 2007	8/90	5/90		23.2 %	1.66 [0.52, 5.28]
Yilmaz 2006	18/65	20/60		76.8 %	0.77 [0.36, 1.64]
Total (95% CI)	**155**	**150**		**100.0 %**	**0.97 [0.52, 1.83]**

Total events: 26 (hCG), 25 (no hCG)

Heterogeneity: Chi^2 = 1.19, df = 1 (P = 0.27); I^2 =16%

Test for overall effect: Z = 0.08 (P = 0.93)

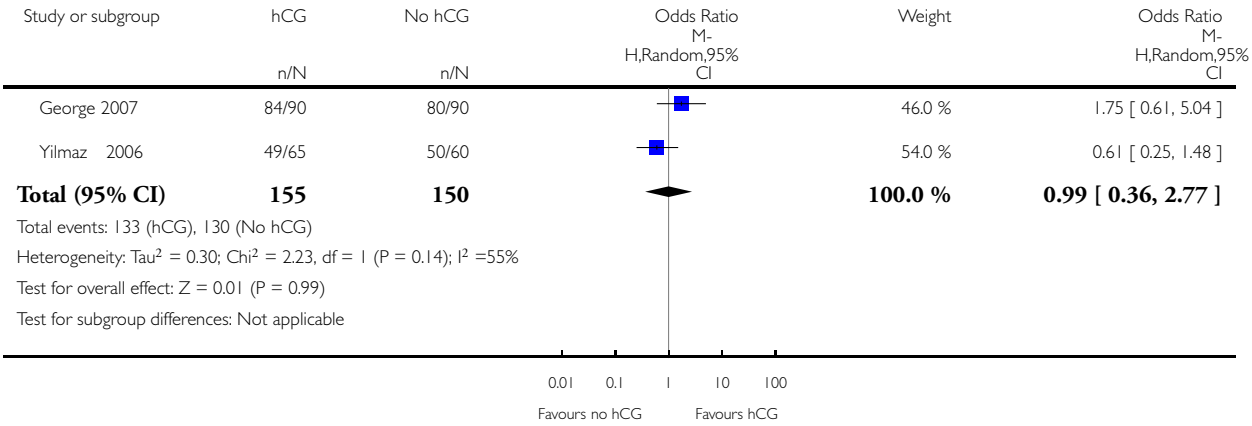
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), Outcome 2 Ovulation rate per woman randomly assigned.

Review: Ovulation triggers in anovulatory women undergoing ovulation induction

Comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles)

Outcome: 2 Ovulation rate per woman randomly assigned

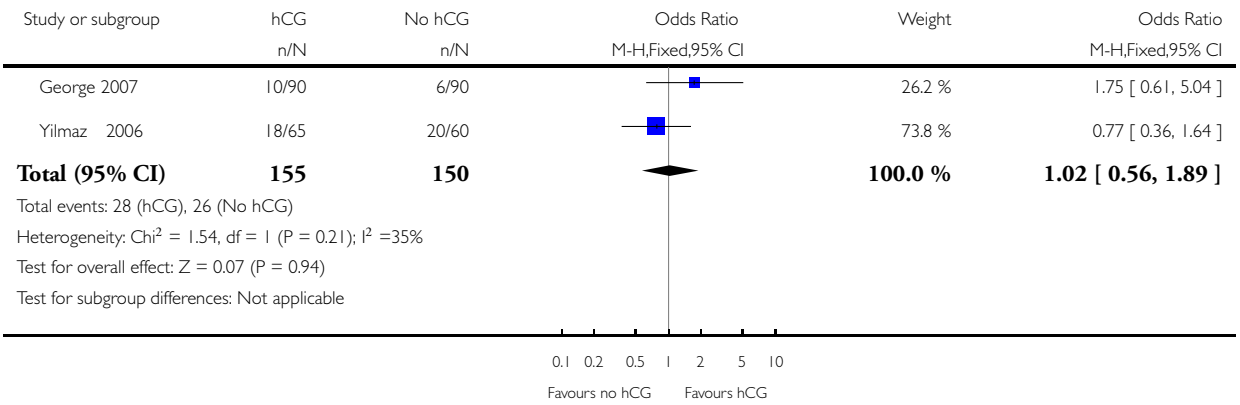


Analysis 1.3. Comparison 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), Outcome 3 Clinical pregnancy rate per woman randomly assigned.

Review: Ovulation triggers in anovulatory women undergoing ovulation induction

Comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles)

Outcome: 3 Clinical pregnancy rate per woman randomly assigned

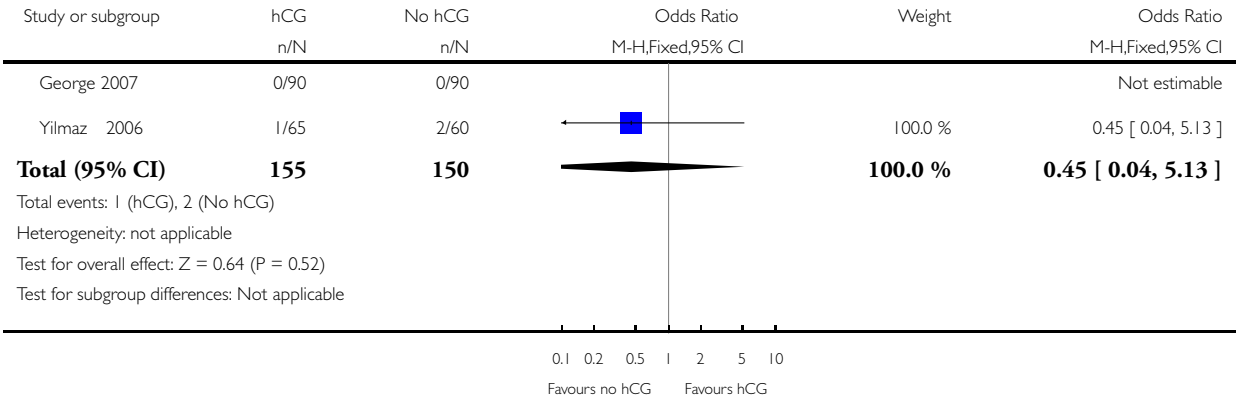


Analysis 1.4. Comparison 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), Outcome 4 Multiple pregnancy rate per woman randomly assigned.

Review: Ovulation triggers in anovulatory women undergoing ovulation induction

Comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles)

Outcome: 4 Multiple pregnancy rate per woman randomly assigned



Analysis 1.5. Comparison 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), Outcome 5 Miscarriage rate per clinical pregnancy.

Review: Ovulation triggers in anovulatory women undergoing ovulation induction

Comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles)

Outcome: 5 Miscarriage rate per clinical pregnancy

Study or subgroup	hCG n/N	No hCG n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
George 2007	2/10	1/6		52.8 %	1.25 [0.09, 17.65]
Yilmaz 2006	1/18	1/20		47.2 %	1.12 [0.06, 19.28]
Total (95% CI)	**28**	**26**		**100.0 %**	**1.19 [0.17, 8.23]**

Total events: 3 (hCG), 2 (No hCG)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 0.17 (P = 0.86)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles), Outcome 6 Preterm delivery rate per woman randomly assigned.

Review: Ovulation triggers in anovulatory women undergoing ovulation induction

Comparison: 1 Human chorionic gonadotrophin versus no treatment (in clomiphene-induced cycles)

Outcome: 6 Preterm delivery rate per woman randomly assigned

Study or subgroup	hCG n/N	No hCG n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
George 2007	0/90	0/90			Not estimable
Yilmaz 2006	0/65	1/60		100.0 %	0.30 [0.01, 7.58]
Total (95% CI)	**155**	**150**		**100.0 %**	**0.30 [0.01, 7.58]**

Total events: 0 (hCG), 1 (No hCG)

Heterogeneity: not applicable

Test for overall effect: Z = 0.73 (P = 0.47)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. MDSG search strategy

KG1391 Menstrual Disorders and Subfertility database search 14.11.13
Keywords CONTAINS “anovulation” or “amenorrhea”or “amenorrhoea ”or “PCOS”or “PCOS”or “polycystic ovary syndrome” or Title CONTAINS “anovulation” or “amenorrhea”or “amenorrhoea ”or “PCOS”or “PCOS”or “polycystic ovary syndrome”
AND
Keywords CONTAINS “ovulation trigger”or “trigger”or “hCG”or “urinary HCG”or “uHCG”or “rh-LH”or “recombinant LH”or“recombinant HCG”or “GnRH agonist”or“GnRH a”or“GnRH agonists”or “GnRHa”or “Gonadotrophin releasing agonist”or“gonadotropin releasing hormone agonist” or Title CONTAINS “ovulation trigger”or “trigger”or “hCG”or “urinary HCG”or “uHCG”or “rh-LH”or “recombinant LH”or“recombinant HCG”or “GnRH agonist”or“GnRH a”or“GnRH agonists”or “GnRHa”or “Gonadotrophin releasing agonist”or“gonadotropin releasing hormone agonist”

Appendix 2. CENTRAL search strategy

1 exp Anovulation/ (97)
2 anovulat$.tw. (308)
3 amenorrhea/ or oligomenorrhea/ (257)
4 amenorrh$.tw. (693)
5 oligomenorrh$.tw. (59)
6 Polycystic Ovary Syndrome/ (684)
7 pcos.tw. (707)
8 Polycystic Ovar$.tw. (1055)
9 pcod.tw. (23)
10 or/1-9 (2084)
11 trigger$.tw. (2240)
12 exp Chorionic Gonadotropin/ (601)
13 HCG.tw. (1015)
14 uhcg.tw. (10)
15 rhcg.tw. (26)
16 exp Luteinizing Hormone/ (1408)
17 Human Chorionic Gonadotrop?in$.tw. (629)
18 rLH.tw. (33)
19 recombinant LH.tw. (56)
20 Recombinant Luteini?ing Hormone$.tw. (22)
21 GnRH A.tw. (1108)
22 buserelin.tw. (267)
23 leuprorelin.tw. (89)
24 nafarelin.tw. (102)
25 triptorelin.tw. (167)
26 gnrh agonist$.tw. (673)
27 gonadotrop?in releasing hormone agonist$.tw. (450)
28 or/11-27 (5894)
29 10 and 28 (446)

30 limit 29 to yr="2012 -Current" (5)

Appendix 3. MEDLINE search strategy

1 exp Anovulation/ (1994)
2 anovulat$.tw. (4604)
3 amenorrhea/ or oligomenorrhea/ (9395)
4 amenorrh$.tw. (12096)
5 oligomenorrh$.tw. (1173)
6 Polycystic Ovary Syndrome/ (10275)
7 pcos.tw. (6166)
8 Polycystic Ovar$.tw. (10552)
9 pcod.tw. (261)
10 or/1-9 (31138)
11 trigger$.tw. (180779)
12 exp Chorionic Gonadotropin/ (29316)
13 HCG.tw. (21316)
14 uhcg.tw. (19)
15 rhcg.tw. (173)
16 exp Luteinizing Hormone/ (44744)
17 Human Chorionic Gonadotrop?in$.tw. (15232)
18 rLH.tw. (281)
19 recombinant LH.tw. (128)
20 Recombinant Luteini?ing Hormone$.tw. (50)
21 GnRH A.tw. (935)
22 buserelin.tw. (1271)
23 leuprorelin.tw. (352)
24 nafarelin.tw. (253)
25 triptorelin.tw. (587)
26 gnrh agonist$.tw. (3620)
27 gonadotrop?in releasing hormone agonist$.tw. (2158)
28 or/11-27 (261679)
29 10 and 28 (5873)
30 randomized controlled trial.pt. (390648)
31 controlled clinical trial.pt. (89952)
32 randomized.ab. (306122)
33 randomised.ab. (67265)
34 placebo.tw. (168269)
35 clinical trials as topic.sh. (175506)
36 randomly.ab. (216624)
37 trial.ti. (132003)
38 (crossover or cross-over or cross over).tw. (63117)
39 or/30-38 (980010)
40 exp animals/ not humans.sh. (4062546)
41 39 not 40 (905465)
42 29 and 41 (562)
43 (2012$ or 2013$).ed. (2071776)
44 42 and 43 (51)

Appendix 4. EMBASE search strategy

1 exp anovulation/ (4027)
2 anovulat$.tw. (5129)
3 exp "amenorrhea and oligomenorrhea"/ or exp secondary amenorrhea/ or exp amenorrhea/ or exp primary amenorrhea/ or exp hypothalamic amenorrhea/ (22059)
4 exp oligomenorrhea/ (2065)
5 amenorrh$.tw. (13503)
6 oligomenorrh$.tw. (1440)
7 exp ovary polycystic disease/ (16746)
8 pcos.tw. (8421)
9 Polycystic Ovar$.tw. (13421)
10 pcod.tw. (318)
11 or/1-10 (46257)
12 trigger$.tw. (200960)
13 exp chorionic gonadotropin/ (37791)
14 HCG.tw. (24380)
15 uhcg.tw. (32)
16 rhcg.tw. (247)
17 Human Chorionic Gonadotrop?in$.tw. (15453)
18 exp luteinizing hormone/ (48348)
19 rLH.tw. (333)
20 recombinant LH.tw. (165)
21 Recombinant Luteini?ing Hormone$.tw. (59)
22 GnRH A.tw. (1073)
23 buserelin.tw. (1484)
24 leuprorelin.tw. (489)
25 nafarelin.tw. (333)
26 triptorelin.tw. (772)
27 gnrh agonist$.tw. (4608)
28 gonadotrop?in releasing hormone agonist$.tw. (2384)
29 or/12-28 (294983)
30 11 and 29 (8708)
31 Clinical Trial/ (889814)
32 Randomized Controlled Trial/ (360008)
33 exp randomization/ (63887)
34 Single Blind Procedure/ (18506)
35 Double Blind Procedure/ (118651)
36 Crossover Procedure/ (38971)
37 Placebo/ (228745)
38 Randomi?ed controlled trial$.tw. (96241)
39 Rct.tw. (12965)
40 random allocation.tw. (1307)
41 randomly allocated.tw. (19937)
42 allocated randomly.tw. (1936)
43 (allocated adj2 random).tw. (736)
44 Single blind$.tw. (14075)
45 Double blind$.tw. (141646)
46 ((treble or triple) adj blind$).tw. (337)
47 placebo$.tw. (197236)
48 prospective study/ (254724)
49 or/31-48 (1388958)
50 case study/ (22252)

51 case report.tw. (255944)
52 abstract report/ or letter/ (892416)
53 or/50-52 (1165147)
54 49 not 53 (1351656)
55 30 and 54 (1421)
56 (2012$ or 2013$).em. (2687795)
57 55 and 56 (198)

Appendix 5. PsycINFO search strategy

1 exp Ovulation/ (292)
2 anovulat$.tw. (117)
3 (ovar$ adj2 stimulat$).tw. (56)
4 ovulat$.tw. (1210)
5 or/1-4 (1351)
6 trigger$.tw. (20256)
7 hcg.tw. (68)
8 human chorionic gonadotrophin$.tw. (8)
9 human chorionic gonadotropin$.tw. (68)
10 rhcg.tw. (2)
11 rlh.tw. (13)
12 gnrh agonist.tw. (42)
13 recombinant lh.tw. (0)
14 Recombinant Luteinizing Hormone.tw. (0)
15 gonadotrophin releasing hormone agonist.tw. (2)
16 gonadotropin releasing hormone agonist.tw. (35)
17 or/6-16 (20434)
18 5 and 17 (54)
19 limit 18 to yr="2012 -Current" (12)

WHAT'S NEW

Last assessed as up-to-date: 18 November 2013.

Date	Event	Description
21 March 2014	Review declared as stable	As no further studies are expected, this review will no longer be updated

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 3, 2008

Date	Event	Description
10 December 2013	New search has been performed	Review updated
10 December 2013	New citation required but conclusions have not changed	New author added; search updated; no new trials found; methods updated; plain language summary revised; conclusions unchanged
15 November 2011	Amended	Converted to new review format Dr Mohan S Kamath joined team as new author.
26 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

KG conceived of and drafted the original review protocol, and RN and PT helped write the protocol.

KG and RN independently selected trials, assessed quality and extracted data for the original review. PT and MSK checked extracted data, independently assessed study quality for this update and prepared Summary of findings tables. KG, MSK, RN and PT helped update this review, and all review authors approved the final version.

DECLARATIONS OF INTEREST

KG and RN are authors of a published randomised trial (George 2007) that is included in this review. The other review authors (MSK and PT) are not aware of any conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Christian Medical College, Vellore, India.

Salary support for MSK and PT; and for KG and RN during completion of the original review

- South Asian Cochrane Network & Centre, India.

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- Bangalore Baptist Hospital, Bangalore, Karnataka, India.

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- Matha Assisted Reproductive Centre, Kottayam, Kerala, India.

Support for RN during the review update

External sources

- Effective Health Care Research Consortium, UK.

Via a programme grant from UKaid (Department of International Development) to the South Asian Cochrane Centre to build capacity in authors from India to undertake systematic reviews

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

MSK joined the review author team for this update. This review update incorporates changes in Cochrane method, such as 'Risk of bias' tables and 'Summary of findings' tables.

INDEX TERMS

Medical Subject Headings (MeSH)

Anovulation [*drug therapy]; Chorionic Gonadotropin [therapeutic use]; Clomiphene [therapeutic use]; Fertility Agents, Female [therapeutic use]; Ovulation Induction [*methods]; Randomized Controlled Trials as Topic; Reproductive Control Agents [therapeutic use]

MeSH check words

Female; Humans; Pregnancy