Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques (Review)

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[Intervention Review]

Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

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ABSTRACT

Background

For many subfertile women, assisted reproductive techniques (ART) is the only hope for a pregnancy and live birth. The combined oral contraceptive pill (OCP) given prior to the hormone therapy in an IVF cycle may result in better pregnancy outcomes of ART.

Objectives

To assess whether pre-treatment with combined OCPs, progestogens or estrogens in ovarian stimulation protocols affects outcomes in subfertile couples undergoing ART.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register, The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, PsycINFO. Other electronic resources on the Internet, reference list of relevant articles were also searched as well as the ESHRE abstracts (2008). All these searches were conducted in November 2008.

Selection criteria

Randomised controlled trials of pre-treatment with combined OCP, progestogen or estrogen in subfertile women undergoing IVF/ICSI.

Data collection and analysis

Two authors independently extracted the data and assessed risk of bias. We calculated Peto odds ratios for dichotomous data and weighted mean difference for continuous variables. Authors of trials were contacted in case of missing data.

Main results

No evidence of effect was found with regard to the number of live births when using a pre-treatment. However, the combined OCP in GnRH antagonist cycles, compared to no pre-treatment, is associated with fewer clinical pregnancies (Peto OR 0.69, 95% CI 0.50 to 0.9; P = 0.03) and more days and a higher amount of gonadotrophin therapy (respectively: MD 1.44, 95% CI 1.15 to 1.72; P < 0.00001; and MD 231.14, 95% CI 161.50 to 300.78; P < 0.00001). Also compared to placebo or no pre-treatment, a progestogen pre-treatment in GnRH agonist cycles, is associated with more clinical pregnancies (Peto OR 1.95, 95% CI 1.20 to 3.17; P = 0.007) and fewer ovarian cysts (Peto OR 0.21, 95% CI 0.12 to 0.35; P < 0.00001). At last, in estrogen pre-treated GnRH antagonist cycles, compared to no pre-treatment, more oocytes are retrieved (MD 2.01, 95% CI 1.76 to2.25; P < 0.00001), but a higher amount of gonadotrophin therapy is needed (MD 207.08, 95% CI 167.77 to 246.39; P < 0.00001). For the other outcomes no evidence of effect was found or there were not enough studies available in the subgroup for pooling.

Authors' conclusions

There was evidence of improved pregnancy outcomes with progestogen pre-treatment and poorer pregnancy outcomes with a combined OCP pre-treatment. However, we conclude that major changes in ART protocols should not be made at this time, since the number of overall studies in the subgroups is small and reporting of the major outcomes is inadequate.

PLAIN LANGUAGE SUMMARY

Pre-treatments in IVF/ICSI cycles

In vitro fertilisation (IVF) and intra cytoplasmic sperm injection (ICSI) are important techniques for women who have trouble getting pregnant. IVF and ICSI cycles consist of a few steps. First the woman receives hormone therapy to stimulate her ovaries in producing egg cells. When a few egg cells are mature enough to be fertilized, the woman receives a single hormone injection. This triggers the ovaries to release the egg cells, so they can be gathered by the clinician. The eggs are then fertilised outside the woman's body and become embryos. At last one or two embryos are transferred into the womb.

Before the first step in IVF or ICSI cycles (hormone therapy), a pre-treatment with a combined oral contraceptive pill (OCP) can be given. A combined OCP contains both progestogen and oestrogen. Pre-treatment with a progestogen or oestrogen alone could also be used before the hormone therapy. These pre-treatments suppress the woman's own hormone production. This might improve the woman's response to the hormone therapy in IVF/ICSI cycles. In this way, adverse events such as cyst formation and the number of pregnancy losses might be reduced and pregnancy outcomes might be improved.

The aim of this review is to assess if pre-treatments with a combined OCP or a progestogen or oestrogen influence these outcomes in IVF/ICSI cycles. This is done by pooling results of more than one study, which will hopefully provide a more solid conclusion. We were able to include 23 studies: a reasonable number. However, due to the formation of subgroups, we have only pooled results of five studies maximum.

Pre-treatment with a combined OCP seems to result in fewer clinical pregnancies. More days of gonadotrophin therapy and a higher amount of gonadotrophins are needed. This is mainly important with regard to the financial aspect of the IVF/ICSI treatment. A pre-treatment with progestogen is associated with more clinical pregnancies and fewer ovarian cysts. Ovarian cysts are frequent reasons for cycle cancellation. In oestrogen pre-treated cycles more eggs are retrieved, but a higher amount of gonadotrophin therapy is needed.

A limitation of this review is that most included studies were small and of poor quality.

The need for a pre-treatment with oral contraceptives should be clearly explained to the woman undergoing IVF, because this might be hard to understand when you are trying to get pregnant.

For definitions of terminology see our Glossary.

BACKGROUND

For definitions of terminology see our Glossary.

Description of the condition

For subfertile women, assisted reproductive techniques (ART) such as in vitro fertilisation (IVF) and intra cytoplasmic sperm injection (ICSI) can be a way to achieve pregnancy. Pregnancy and live birth rates are higher with IVF than with expectant management (Pandian 2005).

An IVF cycle has the following stages: ovarian stimulation, oocyte retrieval, fertilisation of the egg and transfer of the embryo. Ovarian stimulation involves the administration of gonadotrophins. These hormones stimulate growth and maturation of the follicle. Gonadotrophins include follicle stimulating hormone (FSH) and luteinising hormone (LH). There are two different gonadotrophin preparations; human menopausal gonadotrophin (hMG) which consists of both FSH and LH, and a more recent therapy, recombinant follicle stimulating hormone (rFSH). There is insufficient evidence of difference between these treatments in ongoing pregnancy or live birth rate and other aspects with relation to IVF (Van Wely 2003).

There are a number of undesirable events associated with gonadotrophin therapy that can complicate treatment and outcomes: ovarian hyperstimulation syndrome, premature LH-surge and multiple pregnancy (Dodson 1989). In some women undergoing IVF therapy these problems occur because the endogenous FSH and LH production is too dominant (Awadalla 1987). Gonadotrophin releasing hormone analogues (GnRHa) have been administered to inhibit the production of endogenous FSH and LH (Dodson 1989; Awadalla 1987). GnRH is a hormone that occurs naturally in the woman's body and that regulates the production of gonadotrophins. There are two different kinds of GnRH analogues: agonists or antagonists. The difference lies in their mechanism of action. GnRH agonists bind to the GnRH-receptors in the pituitary gland and initially stimulate the release of gonadotrophins ('flare-up'). Negative feedback causes a decrease in the number of GnRH-receptors, which results in the release of fewer gonadotrophins. In a traditional treatment protocol, GnRH agonists are administered prior to commencing gonadotrophins, ensuring that the flare-up will be over by the time gonadotrophins are injected. Conversely, GnRH antagonists can be started after gonadotrophin therapy has been administered because they bind competitively to the receptor, causing immediate suppression of the endogenous production of FSH and LH (Tarlatzis 2006). Therefore GnRH analogues can prevent a premature LH-surge and synchronize the follicle cohort.

The authors of a Cochrane Review comparing GnRH agonists with GnRH antagonist cycles, concluded that the use of GnRH antagonists results in a reduction in the incidence of severe ovarian hyperstimulation syndrome and fewer days of GnRH analogue and hMG treatment, however this is at the expense of a statistically significantly (albeit slightly) lowered ongoing pregnancy rate (OR 0.82, 95% CI 0.69 to 0.98, P=0.03) (Al-Inany 2006).

When a few follicles reach maturity after gonadotrophin stimulation and GnRH analogue treatment, human Chorionic Gonadotrophin (hCG) is administered to trigger ovulation and 34 to 36 hours later, oocyte retrieval is undertaken and the egg is fertilised outside the body. Following fertilisation, the embryos are either transferred on day two or three (cleavage stage) or on day five or six (blastocyst stage). Luteal phase support is typically provided as a progestogen or a hCG treatment, or as a combination of both.

Description of the intervention

Oral contraceptive pills (OCP) are widely used by women of different ages to prevent pregnancy. They are also indicated for a range of menstrual and gynaecological conditions, such as acne vulgaris, polycystic ovary syndrome and menorrhagia (Arowojolu 2007; Harwood 2007; Irvine 1999). Combined pills consisting of oestrogen and progestogen reduce the women's own production of FSH and LH by way of a negative feedback (Cohen 1979; Gaspard 1984). The combined OCP suppresses gonadal function and, in the absence of a LH-surge, no flare-up or premature ovulation will occur. Only progestogen has a contraceptive effect (Erkkola 2007). Progestogen has the ability to slow GnRH pulsatility of the pituitary gland, thereby reducing gonadotrophin surges and, according to dose, inhibiting ovulation (Anderson 1990; Erkkola 2007; Le Nestour 1993; Moudgal 1985). Estrogen is added in the combined OCP to regulate the bleeding patterns, though it is also capable of reducing FSH levels (De Ziegler 1998; Le Nestour 1993).

Most of progestogen-only pills do not inhibit ovulation although higher doses of progestogen may do so (Erkkola 2007).

How the intervention might work

The combined oral contraceptive pill (OCP) given prior to gonadotrophin in an in vitro fertilisation cycle assists synchronisation of the follicular development and prevents the occurrence of spontaneous LH-surges (Gonen 1990). Huirne reports similar data as well as a reduction of the occurrence of large follicles prior to day eight (Huirne 2006a). In a further study, both the combined OCP and progestogen have a suppressive effect on LH and FSH secretion. However, oestrogen administration (in a dosage of 4 mg/day) does not suppress serum LH and FSH values (Cédrin-Durnerin 2007).

It is found that the resulting pituitary suppression of combined OCPs in GnRH antagonist cycles is associated with slower follicular growth and lowered serum estradiol levels in the early part of the cycle. This results in a longer duration of rFSH stimulation

and a higher total rFSH consumption than in antagonist cycles without pre-treatment (Cédrin-Durnerin 2007).
Combined oral contraceptive pre-treatment in an ovarian stimulation protocol before IVF can reduce cyst formation, shorten the length of GnRH analogue treatment and reduce the amount of gonadotrophin needed, without negatively affecting the pregnancy rate (Biljan 1998). Pituitary suppression seems to occur earlier with progestogen pre-treatment and fewer ovarian cysts are formed, when compared with no pre-treatment (Engmann 1999). Combined oral contraceptive pre-treatment can be used for scheduling oocyte retrieval on days of the working week, which is important with antagonist cycles (Barmat 2005; Gonen 1990; Huirne 2006). Scheduling is of benefit for the clinicians and people in the laboratory, since these people usually do not work on weekends.

Why it is important to do this review

There is some debate regarding the effects of the combined OCP upon pregnancy rate. Higher rates of clinical pregnancy and live birth have been reported when dual suppression protocols and GnRH analogues were compared to a GnRH analogue protocol without the use of oral contraceptives in non RCTs (Damario 1997; Keltz 2007). However, other non randomised studies have found no evidence of effect with regard to pregnancy rate (Bellver 2007; Galera 2004).
As illustrated, there is a lack of consensus regarding whether pre-treatment with combined oral contraceptives in ovarian stimulation protocols improves rates of pregnancy and live birth. Furthermore, the effects of pre-treatment with progestogen or oestrogen on IVF outcomes is unclear. The results of many smaller randomised controlled trials can be pooled in a systematic review and may provide a more definitive answer regarding the role of the combined oral contraceptive pill, progestogens or estrogens in assisted reproductive therapy.

OBJECTIVES

To determine whether pre-treatment with the combined oral contraceptive pill, a progestogen or an oestrogen in ovarian stimulation protocols affects outcomes in subfertile couples undergoing any form of assisted reproductive therapy.

METHODS

Criteria for considering studies for this review

Types of studies

- Only truly randomised controlled trials (RCTs) were included in this review. We included both published and unpublished studies and we excluded trials with quasi-randomisation.

- Cross-over trials were included in this review, but excluded from analysis unless pre-crossover data are available, as the design is inappropriate in this context.

Types of participants

Women of any age with subfertility, regardless of any cause, undergoing assisted reproductive therapy.
We only excluded two types of participants from this review. The first is women with premature ovarian failure, because these women require a totally different ovarian stimulation protocol. The second is women who participated in ovarian stimulation protocols as oocyte donors.

Types of interventions

1. Pre-treatment with a combined OCP prior to gonadotrophins with or without GnRH analogues (agonist or antagonist) versus no pre-treatment or placebo prior to gonadotrophins with or without GnRH analogues (agonist or antagonist)
2. Pre-treatment with progestogen prior to gonadotrophins with or without GnRH analogues (agonist or antagonist) versus no pre-treatment or placebo prior to gonadotrophins with or without GnRH analogues (agonist or antagonist)
3. Pre-treatment with oestrogen prior to gonadotrophins with or without GnRH analogues (agonist or antagonist) versus no pre-treatment or placebo prior to gonadotrophins with or without GnRH analogues (agonist or antagonist)
4. Pre-treatment with a combined OCP prior to gonadotrophins with or without GnRH analogues (agonist or antagonist) versus pre-treatment with a progestogen prior to gonadotrophins with or without GnRH analogues (agonist or antagonist)
5. Pre-treatment with a combined OCP prior to gonadotrophins with or without GnRH analogues (agonist or antagonist) versus pre-treatment with an oestrogen prior to gonadotrophins with or without GnRH analogues (agonist or antagonist)
6. Pre-treatment with a progestogen prior to gonadotrophins with or without GnRH analogues (agonist or antagonist) versus pre-treatment with an oestrogen prior to gonadotrophins with or without GnRH analogues (agonist or antagonist)

We excluded studies that compare different doses of the same pre-treatment.

Types of outcome measures

Primary outcomes

- Number of live births per woman randomised - *defined as the delivery of a fetus with signs of life after twenty completed weeks of gestational age, counted as live birth event. When there are multiple live births (e.g. twins or triplets), these are counted as one live birth event* (Griffin 2002).

Secondary outcomes

- Number of ongoing pregnancies per woman randomised - *defined as evidence of a gestational sac with fetal heart motion at twelve weeks or later, confirmed with ultrasoun*d. *When there are multiple gestational sacs in one patient, these are counted as one ongoing pregnancy* (Griffin 2002).
- Number of clinical/ongoing pregnancies per woman randomised - *defined as evidence of a gestational sac with fetal heart motion at six weeks or later, confirmed with ultrasound. When there are multiple gestational sacs in one patient, these are counted as one clinical pregnancy* (Griffin 2002).
- Number of oocytes retrieved per woman randomised
- Days of gonadotrophin treatment per woman randomised
- Amount of gonadotrophins administered per woman randomised

Adverse outcomes

- Number of pregnancy loss per woman randomised - *defined as the sum of the number of spontaneous abortions (pregnancy loss before twenty completed weeks of gestation) and the number of stillbirths (pregnancy loss after twenty completed weeks of gestation)* (Griffin 2002).
- Number of women with ovarian cyst formation - *defined as any intraovarian sonolucent structure with a mean diameter of 15 mm or more confirmed with ultrasound at least one week after start pituitary suppression* (Biljan 1998).
- Number of multiple pregnancies per woman randomised - w*hen there are multiple gestational sacs in one patient, these are counted as one multiple pregnancy.*
- Number of ovarian hyperstimulation (OHS) syndrome per woman randomised - *defined as a condition that can occur from drugs used in ART, through stimulating a large number of follicles in the ovary to develop and ovulate (*MDSG Module 2008).

Search methods for identification of studies

We obtained all studies that describe (or might describe) randomised controlled trials of pre-treatment with combined oral contraceptive pills, progestogen or oestrogen therapy prior to GnRH analogues (agonists or antagonists) and gonadotrophins or gonadotrophins alone in women undergoing in vitro fertilisation, using the following search strategies.

Electronic searches

- The Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials has been searched for any relevant trials using the terms 'in vitro fertilization' or 'intracytoplasmic sperm injection' or 'ART' or 'controlled ovarian' AND 'oral contraceptive' or 'combined oral contraceptives' or 'progestogen' or 'oestrogen' in the titles, abstracts and keywords; 1947 -17 November 2008 (Appendix 1).

We searched the following electronic databases using Ovid software:

- Cochrane Central Register of Controlled Trials (CENTRAL); from inception - 17 November 2008 (Appendix 2);
- MEDLINE; 1950 - 17 November 2008 (Appendix 3). We combined this search with the Cochrane highly sensitive search strategy for identifying randomised trials (Higgins 2008);
- EMBASE; 2007 - 17 November 2008 (Appendix 4). We combined this search with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL); 1982 - 17 November 2008 (Appendix 5). We combined this search with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN); and
- PsycINFO; 1806 - 17 November 2008 (Appendix 6).

We did not restrict the search by language. We managed output of these searches with a reference manager, Endnote (EndNote). Through this program, duplicates can be found and removed.

Searching other resources

In addition, we searched some other resources than the electronic databases mentioned above to obtain more relevant trials. We accessed all the web sites on 18 November 2008, except for OpenSIGLE.

- Trial registers for ongoing and registered trials: Current Controlled Trials (http://www.controlled-trials.com), ClinicalTrials.gov (http://clinicaltrials.gov/ct2/home), and The World Health Organisation International Trials Registry Platform Search Portal (http://www.who.int/trialsearch).
- Citation indexes (http://scientific.thomson.com/products/sci).
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed); we combined this search with random control filters for PubMed (Higgins 2008).
- Conference abstracts on the ISI Web of Knowledge (http://isiwebofknowledge.com).
- ClinicalStudyResults provides clinical trial results of marketed pharmaceuticals (http://www.clinicalstudyresults.org).
- Open System for Information on Grey Literature (http://opensigle.inist.fr, accessed on 26 November 2008).
- All the reference lists of the studies obtained with the electronic databases.

- Handsearching of the abstracts of the 24th annual meeting of the European society of human reproduction and embryology in Barcelona (Spain), 6 to 9 July 2008 (ESHRE 2008).

Data collection and analysis

Selection of studies

Two review authors (BS and SvO) independently scanned the titles and abstracts of all the studies found with the search to exclude those which did not meet the inclusion criteria. We discussed any disagreement or doubt, whether a study is eligible for inclusion or not, with a third review author (CF) to achieve consensus. We obtained full text of those RCTs deemed eligible for inclusion where possible, and subjected them to critical appraisal of their risk of bias. Where appropriate, we included them in this systematic review.

Subsequently, we constructed a table of Characteristics of included studies for those trials considered suitable for inclusion. We produced another table, Characteristics of excluded studies, for those that did not satisfy the inclusion criteria. In this table we listed the reasons for exclusion.

Data extraction and management

The review authors (BS and SvO) independently extracted the data using data extraction forms, which we designed for this particular review (Appendix 7; Appendix 8). We resolved any discrepancies by discussion and the help of a third review author (CF).

The data extraction forms included risk of bias criteria and methodological details. The information about the studies is included in the review and presented in the tables of Characteristics of included studies. We managed the data using Review Manager 5 software (RevMan).

We extracted the following information from the studies selected for the review:

Trial characteristics

- Quality of allocation concealment
- Method of randomisation
- Trial design: cross-over or parallel
- Blinding of investigator, patient and outcome assessors
- Details on dropouts and intention-to-treat analysis used
- Presence of power calculation
- Duration, timing and location of the trial (single or multi centre)
- Number of patients randomised, excluded, analysed and lost to follow-up
- Source of funding

Characteristics of participants

- Women's age
- Body Mass Index (BMI)
- Cause of subfertility
- Duration of subfertility
- Previous number of ART treatment cycles
- Poor response to ovarian stimulation

Characteristics of interventions

- Preparations used for pre-treatment, pituitary desensitization and ovarian stimulation
- Dosage of preparations
- Length of each different treatment in days
- Treatment protocol (timing of administration of pre-treatments, gonadotrophins and GnRH analogues)
- Type of protocol (long versus short agonist protocol; single versus multiple antagonist protocol; fixed versus flexible antagonist protocol)

Types of outcome measures

As described above (*see* Criteria for considering studies for this review).

Assessment of risk of bias in included studies

We assessed and reported on the risk of bias of included studies in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) which recommends the explicit reporting of the following domains:

- Sequence generation

Was sequence generation adequate (e.g. use of a random number table, a computer random number generator or coin tossing), inadequate (e.g. use of date of birth or clinical record number) or unclear (insufficient information about the process of sequence generation)?

- Allocation concealment

Was allocation concealment adequate (e.g. use of central allocation or opaque sealed envelopes), inadequate (e.g. use of an open random allocation schedule, date of birth or case record number) or unclear (insufficient information about the process of allocation concealment)?

- Blinding of participants, providers and outcome assessors

Was blinding adequate (e.g. participants and researchers were all blinded and it was unlikely that blinding could have been broken, either participants or some researchers are not blinded but outcome assessment was blinded or no blinding was used but this is not likely to influence outcomes), inadequate (e.g. no blinding or incomplete blinding and outcomes are likely to be influenced by this) or unclear (insufficient information about the process of blinding)?

- Incomplete outcome data

Were outcome data addressed adequately (e.g. there were no missing outcome data, reasons for missing outcome data were unlikely to be related to true outcome or missing outcome data were balanced in numbers across intervention groups), inadequate (e.g. reasons for missing outcome data were likely to be related to true outcome) or unclear (insufficient information about the process of addressing outcome data)?

- Selective outcome reporting

Was the study free of selective reporting? Adequate (e.g. the study protocol is available and all pre-specified outcomes have been reported or the study protocol is not available but it is clear that all pre-specified outcomes have been reported), inadequate (e.g. not all pre-specified primary outcomes have been reported) or unclear (insufficient information about the process of outcome reporting).

- Other sources of bias for RCTs

Was the study free of other bias? Adequate (the study seems to be free of other bias), inadequate (e.g. extreme baseline imbalance, a potential source of bias related to the specific study design used or early stopping) or unclear (insufficient information about other sources of bias).

By using a simple form (Appendix 7; Appendix 8) two review authors (BS and SvO) separately assessed these domains as 'yes' (indicating a low risk of bias), 'unclear' (indicating an uncertain risk of bias) or 'no' (indicating a high risk of bias).

The assessments of the two review authors were compared and we resolved any discrepancies in the interpretation of the risk of bias of a study by discussion with a third review author. We did not automatically exclude any study as a result of a rating of 'Unclear' or 'No'. Where it was unclear, we contacted authors of studies about the methods used and also sought any missing data.

We presented the results of the risk of bias assessment in the tables of Characteristics of included studies within the review, including commentary about each of the domains. This led to an overall assessment of the risk of bias of included studies (Figure 1; Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

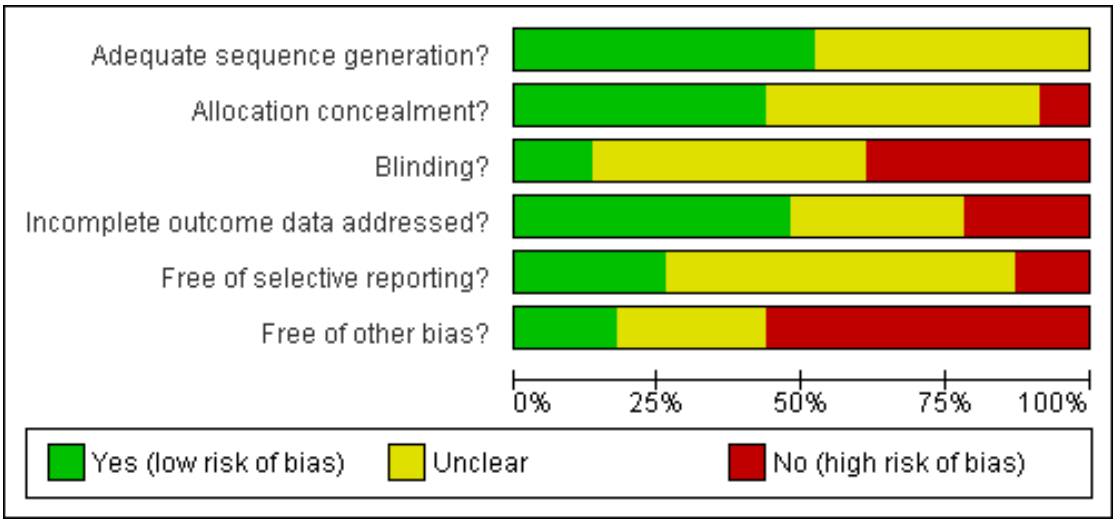
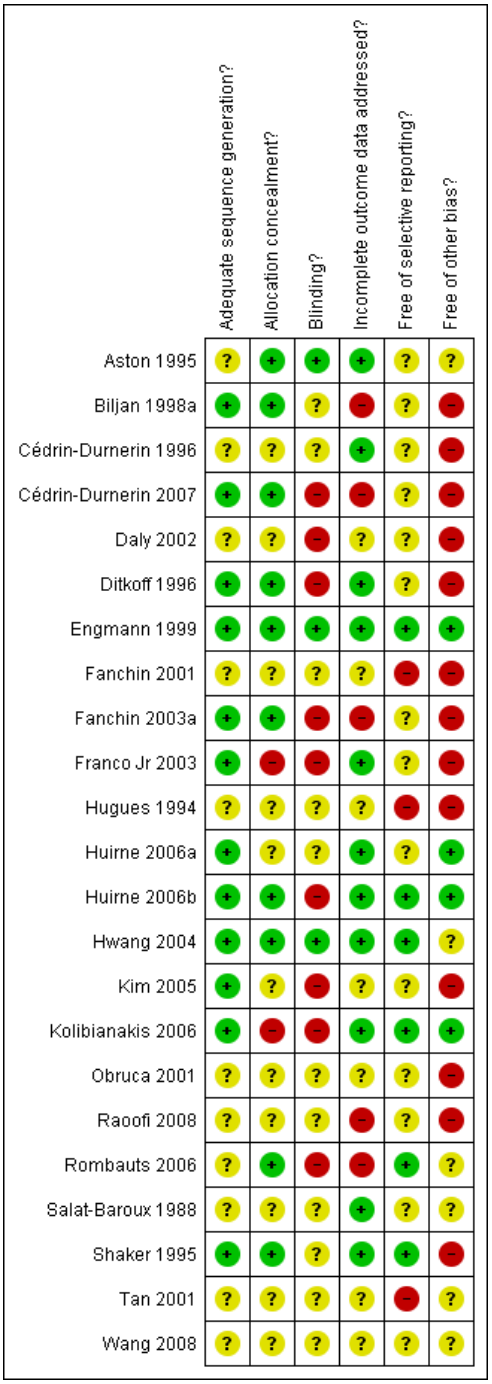


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

For dichotomous data, we expressed results for each study as Peto odds ratios (OR) with 95% confidence intervals (CI). For continuous variables, we reported the data as a weighted mean difference (WMD) with 95% confidence intervals.

Unit of analysis issues

In order to avoid analysis errors, we only pooled data that report outcomes per woman randomised.

Dealing with missing data

In case of missing data in the included studies, we contacted the original investigators by e-mail or post to request relevant missing information. If we did not receive a reply, we sent a reminder to the authors a couple of weeks later. Furthermore, we contacted the members of the MDSG-group to ask if they know any of the authors personally or have contact details.
We reported the data according to intention-to-treat where possible.

Assessment of heterogeneity

Before any meta-analysis was done, we judged whether there was sufficient similarity between the eligible studies in their design and clinical characteristics to ensure that pooling is valid. We assessed statistical heterogeneity in the results of trials by using the Chi^2 test. A low P value (or a large Chi^2 statistic relative to its degree of freedom) will potentially provide evidence of heterogeneity of intervention effects and show that results are not influenced by chance alone (Higgins 2008).
We used the I^2 statistic to assess the impact of the heterogeneity on the meta-analysis. We interpreted the result of the I^2 statistic as follow:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity (Higgins 2008).

If we found marked clinical or statistical heterogeneity (I^2 more than 50%), we explored reasons for this heterogeneity by using sensitivity analysis.

Assessment of reporting biases

To investigate the potential for publication bias, we planned to use a funnel plot, but due to the small number of studies per subgroup this was not possible.

Data synthesis

We carried out statistical analysis using Review Manager 5 (RevMan). We used fixed-effect meta-analysis for combining data. If we found heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we explored this by sensitivity analysis. We planned to do a random-effects meta-analysis if required, but this was not necessary.

Subgroup analysis and investigation of heterogeneity

To reduce heterogeneity between studies, we pooled the data of GnRH agonist and GnRH antagonist cycles separately by performing subgroup analyses on different treatment protocols:

- GnRH agonist in study group versus GnRH agonist in control group
- GnRH antagonist in study group versus GnRH antagonist in control group
- GnRH antagonist in study group versus GnRH agonist in control group
- GnRH agonist in study group versus GnRH antagonist in control group

Furthermore, we did subgroup analysis on low responder patients. Unfortunately, we could only include one trial in each subgroup which made pooling impossible.
Furthermore, we planned to do subgroup analyses on women's age; poor response; agonist long, short and ultra-short protocol; and the duration of pre-treatment. However, due to the small number of included studies per comparison, we were not able to do subgroup analyses on these aspects.

Sensitivity analysis

We planned to use a sensitivity analysis to explore whether the findings from the meta-analysis were dependent on aspects within individual studies deemed eligible for inclusion. Aspects we planned to do a sensitivity analysis on, were random sequence generation, allocation concealment and the overall assessment of risk of bias. Due to the small number of studies in each subgroup, we were unable to do any sensitivity analyses.

RESULTS

Description of studies

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

Results of the search

After searching the electronic databases, we found a total of 1049 studies: 492 studies in the MDSG specialised register of controlled trials, 123 studies in CENTRAL, 350 studies in MEDLINE, 61 studies in EMBASE, 3 studies in CINAHL and 20 studies in PsycINFO. After removing the duplicates and searching other resources, there were approximately 900 studies left. Around 200 studies seemed eligible for inclusion, after the first screening of titles and abstracts and we were able to include 23 studies in this review.

Included studies

The following is a summary of the methods, participants, interventions and outcomes of all the included studies. Full details of these domains (for each study separately) can be found in the tables of Characteristics of included studies.

Methods in included studies

The main analyses were based on 23 trials, which involved a total of 2596 women randomised to treatment.

The three largest trials included in this review were Kolibianakis 2006 (504 women), Rombauts 2006 (351 women) and Huirne 2006a (182 women). The smallest trial was Fanchin 2001 with fourteen women randomised. Four trials used a cross-over design, of which only two reported pre-cross-over data (Daly 2002; Wang 2008). The other two studies can not be used in our analysis since only post-cross-over data is available (Cédrin-Durnerin 1996; Fanchin 2001). The other nineteen trials used a parallel design. Four studies were conducted in multiple centres, according to their articles (Cédrin-Durnerin 2007; Huirne 2006a; Huirne 2006b; Rombauts 2006).

The trials took place in (or authors came from): France (six trials: Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Fanchin 2001; Fanchin 2003a; Hugues 1994; Salat-Baroux 1988); United Kingdom (two trials: Aston 1995; Shaker 1995); Canada (two trials: Biljan 1998a; Tan 2001); United Kingdom and Canada (Engmann 1999); United States of America (two trials: Daly 2002; Ditkoff 1996); Austria (Obruca 2001); Belgium (Kolibianakis 2006); Brazil (Franco Jr 2003); China (Wang 2008); Iran (Raoofi 2008); South Korea (Kim 2005); Taiwan (Hwang 2004); Australia, Denmark, Jordan and Norway (Rombauts 2006); The Netherlands and Belgium (Huirne 2006b); and The Netherlands, Belgium, France and Austria (Huirne 2006a).

Of the 23 included studies, ten performed and adhered a power calculation (Aston 1995; Biljan 1998a; Engmann 1999; Fanchin 2003a; Huirne 2006a; Huirne 2006b; Hwang 2004; Kim 2005; Kolibianakis 2006; Rombauts 2006). Seven studies did not adhere a power calculation (Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Ditkoff 1996; Franco Jr 2003; Raoofi 2008; Salat-Baroux 1988; Shaker 1995) and of five studies this is unclear, because there was only an abstract available (Daly 2002; Fanchin 2001; Hugues 1994; Obruca 2001; Tan 2001). Of one trial it was unclear, because we only have the article in a foreign language of which only the most important sections were translated (Wang 2008).

Only one of the included trials seems to have used a true intention-to-treat analysis (Kim 2005), which means that all outcomes of all the randomised women are used in the final analysis.

Of the other included trials it seems that this was not done. Nine trials analysed data of all randomised women for a few of the outcomes, but not for all (for example, the table of baseline characteristics is usually constructed by analysing data of all randomised women, but the number of oocytes retrieved is calculated from data of only women that reached oocyte retrieval).

Six trials used no intention-to-treat analysis for any of their outcomes (Aston 1995; Engmann 1999; Fanchin 2003a; Franco Jr 2003; Kolibianakis 2006; Rombauts 2006) and of the other seven trials it is unclear whether they used an intention-to-treat analysis because there is not enough information available (Daly 2002; Fanchin 2001; Hugues 1994; Obruca 2001; Raoofi 2008; Shaker 1995; Tan 2001).

Participants in included studies

Inclusion criteria

Of the 23 studies, 18 studies included women with a regular IVF/ICSI indication, five trials only included women who had a special indication for IVF. Two trials only included women who are poor responders (Kim 2005; Wang 2008). One trial only included women with limited ovarian reserve (Daly 2002). Another trial only included women with polycystic ovary syndrome (Hwang 2004) and the last trial only included women if they had an ovarian cyst of over 5 mm in diameter or an endometrial thickness of over 5 mm and serum E_2 concentration > 100 pmol/L after fourteen days of GnRH agonist treatment (Shaker 1995).

Thirteen of the studies mentioned an age limit as an inclusion criteria. Four studies only included women less than 38 years of age (Cédrin-Durnerin 2007; Franco Jr 2003; Huirne 2006b; Salat-Baroux 1988). Five studies only included women less than 39 years of age (Fanchin 2003a; Huirne 2006a; Hwang 2004; Kolibianakis 2006; Rombauts 2006). The other four studies used age limits above 40 years of age: one study used an upper limit of 41 years of age (Daly 2002), two studies an upper limit of 42 years of age (Cédrin-Durnerin 1996; Kim 2005) and one study used an upper limit of 44 years of age (Engmann 1999). Lower limits were defined in five of these 13 studies: four studies used a lower limit of 18 years of age (Engmann 1999; Huirne 2006a; Huirne 2006b; Rombauts 2006), and for one study the lower age limit was 28 years of age (Kim 2005). Ten studies did not mention an age limit in their description of the women.

Other common inclusion criteria were the presence of regular menstrual cycles (Cédrin-Durnerin 2007; Fanchin 2003a; Huirne

2006b; Rombauts 2006) and a BMI of less than 29 or 30 kg/m^2 (Cédrin-Durnerin 2007; Fanchin 2003a; Huirne 2006b; Kolibianakis 2006; Rombauts 2006).

Exclusion criteria

Five studies excluded women with an evidence of poor response. Two studies defined this as any previous ART cycles with less than three oocytes (Huirne 2006a; Huirne 2006b), the first study also excluded women if they had a history of three or more consecutive ART cycles without a clinical pregnancy. Another study defined this as less than five oocytes in a previous IVF attempt or less than five follicles in a spontaneous cycle (Cédrin-Durnerin 2007), and one study defined this as more than three unsuccessful controlled ovarian stimulation cycles or a history of low or no ovarian response during FSH/hMG (Rombauts 2006). One study did not mention how they defined poor response to ovarian stimulation in their trial (Kolibianakis 2006).

Other common exclusion criteria were: a high baseline serum FSH level (Cédrin-Durnerin 2007; Ditkoff 1996; Engmann 1999; Huirne 2006b; Hwang 2004; Kolibianakis 2006), the evidence of ovarian cysts or endometrioma (Aston 1995; Engmann 1999; Kolibianakis 2006) and polycystic ovary syndrome (Huirne 2006b; Rombauts 2006).

Interventions in included studies

Three of the 23 studies have more than two study arms and can be used in more than one comparison (Cédrin-Durnerin 2007; Kim 2005; Rombauts 2006).

Combined OCP versus placebo or no pre-treatment

In eleven trials (with a total of thirteen comparisons) the study group was given a pre-treatment with a combined OCP, while the control group received no pre-treatment. None of these studies used a placebo in the control group. Seven trials used ethinyl estradiol as the oestrogen component in a daily dose of 30 μg (Cédrin-Durnerin 2007; Huirne 2006a; Huirne 2006b; Kolibianakis 2006; Obruca 2001; Raoofi 2008; Rombauts 2006). Five trials used 150 μg desogestrel daily (Cédrin-Durnerin 2007; Kolibianakis 2006; Obruca 2001; Raoofi 2008; Rombauts 2006) and two trials used 150 μg levonorgestrel daily as the progestogen component (Huirne 2006a; Huirne 2006b). One study used Diane-35, which contains 35 μg ethinyl estradiol and 2 mg cyproterone acetate (Hwang 2004). From three studies there are not enough data available on the type of combined OCP used (Biljan 1998a; Kim 2005; Wang 2008).

The starting days of pre-treatment in all eleven trials varied from cycle day one to five. Five studies started the combined OCP pre-treatment on cycle day one (Biljan 1998a; Kolibianakis 2006; Obruca 2001; Raoofi 2008; Rombauts 2006). Two studies started the pre-treatment on cycle day two or three (Cédrin-Durnerin 2007; Huirne 2006b). One study started the pre-treatment on a variable cycle day from one to five (Huirne 2006a). Another study started the pre-treatment on cycle day five (Hwang 2004). From two studies there are not enough data available on the start day of pre-treatment (Kim 2005; Wang 2008).

The duration of pre-treatment in all eleven trials varied from fourteen days to three consecutive cycles. Three studies used a fixed duration of fourteen days of pre-treatment (Biljan 1998a; Kolibianakis 2006; Raoofi 2008). Two studies used a variable duration of pre-treatment of 14 to 28 days (Huirne 2006b; Rombauts 2006). Three other studies used a variable duration of around two or three weeks minimum to around four weeks maximum (Cédrin-Durnerin 2007, 15 to 21 days; Obruca 2001, 18 to 28 days; Huirne 2006a, 21 to 28 days). The longest pre-treatment duration of three consecutive cycles was used by Hwang 2004. From two studies there are not enough data available on the duration of pre-treatment (Kim 2005; Wang 2008).

Two studies used agonists in both treatment groups. One study used buserelin acetate (long protocol) (Biljan 1998a) and the other used a depot of triptorelin acetate (Raoofi 2008).

Six studies used antagonists in both treatment groups. Three of these studies used ganirelix acetate (Cédrin-Durnerin 2007; Kolibianakis 2006; Rombauts 2006), one study used cetrorelix acetate (Obruca 2001), one used antide (Huirne 2006b) and the other one did not mention which GnRH antagonist was used (Kim 2005).

Four trials used an antagonist in the study group and an agonist in the control group. Two used cetrorelix acetate as antagonist and buserelin acetate as agonist (Huirne 2006a; Hwang 2004). One used ganirelix acetate as antagonist and nafarelin acetate as agonist (Rombauts 2006). The other study did not mention which GnRH analogues were used (Kim 2005).

One trial used an agonist in the study group and an antagonist in the control group, but did not mention which GnRH analogues were used (Wang 2008).

Progestogen versus placebo or no pre-treatment

In eight trials the study group was given a pre-treatment with a progestogen, while the control group received placebo (Aston 1995) or no pre-treatment. Five studies used norethisterone 10 mg daily (Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Ditkoff 1996; Engmann 1999; Hugues 1994), one study used medroxyprogesterone acetate 10 mg daily (Aston 1995) and one study used ethynodiol acetate 4 mg daily (Salat-Baroux 1988). Another study used a single injection of 100 mg, but did not mention what type of progestogen they used (Shaker 1995).

The starting days of pre-treatment in all eight trials varied from cycle day one to nineteen. Two studies started the pre-treatment with progestogen on cycle day one (Ditkoff 1996; Engmann 1999). Three other studies started the pre-treatment on cycle day fifteen (Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Salat-Baroux

1988). One study started the pre-treatment on cycle day sixteen or seventeen (Shaker 1995) and another study on cycle day nineteen (Aston 1995). From one study there are not enough data available on the start day of pre-treatment (Hugues 1994).

The duration of progestogen pre-treatment varied from one day to twenty days. In one study the women received one single injection (Shaker 1995). One study used a duration of pre-treatment of five days (Engmann 1999). Another study used a duration of seven days (Aston 1995) and one study of eight days (Ditkoff 1996). Two trials used a variable duration of ten to fifteen days (Cédrin-Durnerin 2007; Hugues 1994) and one trial had a variable duration of eleven to seventeen days (Salat-Baroux 1988). At last, there was one study that used a variable duration of twelve to twenty days (Cédrin-Durnerin 1996).

Six trials used an agonist in both treatment groups. Three studies used buserelin acetate (Aston 1995; Engmann 1999; Shaker 1995), one study used triptorelin (Cédrin-Durnerin 1996), one study used leuprolide acetate (Ditkoff 1996) and another study used dTRP6-LHRH (Hugues 1994).

One trial used an antagonist (ganirelix acetate) in both treatment groups (Cédrin-Durnerin 2007).

One trial did not use GnRH analogues for pituitary desensitization. Women that participated in this study only received pure FSH and hMG (Salat-Baroux 1988).

Estrogen versus placebo or no pre-treatment

In three trials the study group was given a pre-treatment with oestrogen, while the control group received no pre-treatment. Two studies used micronized 17-βE_2 (Cédrin-Durnerin 2007; Fanchin 2003a) and one study used estradiol valerate (Franco Jr 2003). All these studies used a dosage of 4 mg daily.

The starting days of pre-treatment in all three trials varied from cycle day 15 to 21. One study started the pre-treatment on cycle day 20 (Fanchin 2003a) and one on cycle day 21 (Franco Jr 2003). The other study started the pre-treatment ten days before the presumed menses (Cédrin-Durnerin 2007).

The duration of pre-treatment in all three trials varied from ten to seventeen days. In one study the duration varied from ten to fifteen days (Cédrin-Durnerin 2007). The other two studies used a fixed duration of pre-treatment of eleven days (Fanchin 2003a) and fourteen days (Franco Jr 2003).

Two trials used an antagonist in both treatment groups, one trial used ganirelix acetate (Cédrin-Durnerin 2007) and the other used cetrorelix acetate (Fanchin 2003a).

One trial used an antagonist (ganirelix acetate) in the study group and an agonist (nafarelin acetate) in the control group (Franco Jr 2003).

Combined OCP versus progestogen

There was only one study that compared a combined OCP with progestogen (Cédrin-Durnerin 2007). The women in the combined OCP group received ethinyl estradiol 30 μg and desogestrel 150 μg daily and the women in the progestogen group received norethisterone 10 mg daily. This study started the combined OCP pre-treatment on cycle day two or three with a duration of 15 to 21 days. The progestogen pre-treatment was started on cycle day fifteen with a duration of ten to fifteen days. Both groups received a GnRH antagonist (ganirelix acetate).

Combined OCP versus oestrogen

In two trials a pre-treatment of combined OCP was compared with a pre-treatment of oestrogen. One trial used ethinyl estradiol 30 μg and desogestrel 150 μg daily as a combined OCP and micronized 17-βE_2 4 mg daily as oestrogen pre-treatment (Cédrin-Durnerin 2007). The combined OCP pre-treatment started on cycle day two or three with a duration of 15 to 21 days. The oestrogen pre-treatment started ten days before the presumed menses with a duration of ten to fifteen days and both groups received the GnRH antagonist ganirelix acetate .

The other study did not mention which combined OCP was used, but used two mg ethinyl estradiol as an oestrogen pre-treatment (Daly 2002). This study only described that the oestrogen pre-treatment was administered in the luteal phase of the preparation cycle, but did not report about exact starting days and durations of pre-treatment. The combined OCP group received a GnRH agonist (leuprolide acetate) and the oestrogen group received a GnRH antagonist (ganirelix acetate).

Progestogen versus oestrogen

There was only one study that compared progestogen with oestrogen (Cédrin-Durnerin 2007). The women in the progestogen group received norethisterone ten mg daily and the women in the oestrogen group received micronized 17-βE_2 4 mg daily. This study started the progestogen pre-treatment on cycle day fifteen with a duration of ten to fifteen days. The oestrogen pre-treatment started ten days before the presumed menses with also a duration of ten to fifteen days. Both groups received a GnRH antagonist (ganirelix acetate).

Outcomes in included studies

Primary outcome

The number of live births was reported in seven studies (Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Ditkoff 1996; Engmann 1999; Franco Jr 2003; Huirne 2006a; Kim 2005).

Secondary outcomes

The number of ongoing pregnancies was reported in eight studies. This was defined as a positive heart activity at a gestational age of twelve weeks by three studies (Huirne 2006a; Huirne 2006b; Kim 2005). One study used the same definition but did not mention when they performed the ultrasound scan (Ditkoff 1996). Two studies defined this as a pregnancy developing beyond twelve weeks (Cédrin-Durnerin 2007; Kolibianakis 2006) and one study defined this as a pregnancy assessed by ultrasound at twelve to sixteen weeks or later (Rombauts 2006). The last study defined ongoing pregnancy as a viable pregnancy and did not mention how they assessed this (Daly 2002).

The number of clinical pregnancies was reported in eighteen studies. Five studies defined clinical pregnancy as the presence of one or more fetal hearts confirmed with ultrasound (US), performed at least four weeks after embryo transfer (Biljan 1998a; Fanchin 2003a, US after six weeks; Franco Jr 2003; Kim 2005; Raoofi 2008). Two other studies used the same definition, but one of these also included the fetal sacs without heart activity (Huirne 2006a) and the other performed the US scan at seven weeks after embryo transfer (Hwang 2004). One study defined clinical pregnancy as the presence of one or more intrauterine sacs confirmed with US, at a gestational age of six weeks (Huirne 2006b). Of one study we used a positive pregnancy test with evidence of a gestational sac to define clinical pregnancy, because no clinical or ongoing pregnancy rate was available (Engmann 1999). Another study defined clinical pregnancy as the evidence of a clinical gestational sac (Ditkoff 1996). Of the other eight studies it was not clear how they defined this outcome (Aston 1995; Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Daly 2002; Obruca 2001; Salat-Baroux 1988; Shaker 1995; Wang 2008). If no clinical pregnancy rates were reported, we used the ongoing pregnancy rates (if available) for our analysis.

The number of oocytes retrieved was reported in fourteen studies (Biljan 1998a; Cédrin-Durnerin 2007; Ditkoff 1996; Franco Jr 2003; Huirne 2006a; Huirne 2006b; Hwang 2004; Kim 2005; Obruca 2001; Raoofi 2008; Rombauts 2006; Salat-Baroux 1988; Shaker 1995; Wang 2008). One study only mentioned the number of cumulus-oocyte complexes (Kolibianakis 2006) and three studies the number of mature oocytes or follicles (Cédrin-Durnerin 1996; Engmann 1999; Fanchin 2003a), but we assumed that this means the same as the number of oocytes retrieved and therefore we pooled the data of these studies.

The number of days of gonadotrophin treatment was reported in twelve studies (Biljan 1998a; Ditkoff 1996; Engmann 1999; Franco Jr 2003; Huirne 2006a; Huirne 2006b; Hwang 2004; Kim 2005; Kolibianakis 2006; Rombauts 2006; Shaker 1995; Wang 2008).

The amount of gonadotrophins administered in IU was reported by eight studies (Cédrin-Durnerin 2007; Fanchin 2003a; Franco Jr 2003; Huirne 2006a; Huirne 2006b; Kim 2005; Kolibianakis 2006; Rombauts 2006). Another seven studies reported the amount of gonadotrophins administered in the number of ampoules used, but we can not use these data in our analysis (Biljan 1998a; Cédrin-Durnerin 1996; Ditkoff 1996; Engmann 1999; Hwang 2004; Shaker 1995; Wang 2008).

Adverse outcomes

The number of pregnancy losses was reported by eight studies. One study described this as the proportion of patients with initially positive hCG in whom pregnancy failed to develop before 12 weeks of gestation (Kolibianakis 2006). The other seven studies did not describe a definition (Daly 2002; Engmann 1999; Franco Jr 2003; Hwang 2004; Kim 2005; Rombauts 2006; Salat-Baroux 1988).

The number of women with ovarian cysts was reported by eight studies. Of one study we used the number of functional ovarian cysts with a diameter of 10 mm or more, measured after one week of GnRH agonist treatment (Engmann 1999). Four studies defined an ovarian cyst as an intraovarian sonolucent structure with a mean diameter of 14 mm or more, measured after seven to twelve days of pituitary suppression (Aston 1995, after twelve days; Biljan 1998a, after seven days; Ditkoff 1996, after eight days; Franco Jr 2003, not reported). One study reported ovarian cysts when they reached a diameter of more than 28 mm, measured seven and fourteen days after pituitary suppression (Raoofi 2008). One study did not mention how they defined ovarian cyst formation and when they measured this (Huirne 2006b).

One study only reported cyst formation as reason for cycle cancellation, but it is unclear if there were more cysts formed that did not lead to cycle cancellation (Salat-Baroux 1988). We did not use these data in our analysis.

The number of multiple pregnancies was reported by five studies. One study defined this as multiple clinical pregnancies (Huirne 2006a). Another study described the number of ongoing or live born twin pregnancies (Hwang 2004). Three studies did not describe when the number of multiple pregnancies was measured (Cédrin-Durnerin 2007; Franco Jr 2003; Kim 2005).

The number of OHS syndrome was reported by three studies. One study used the WHO classification criteria to diagnose OHS syndrome and divided the women in categories of mild (grade I), moderate (grade II) or severe (grade III) (Rombauts 2006), the other two studies did not mention how they diagnosed OHS syndrome (Franco Jr 2003; Hwang 2004).

Excluded studies

We referred to a total of 67 studies that describe pre-treatments with combined OCPs, progestogens or estrogens, but which were not eligible for inclusion for various reasons. Some of the following studies had multiple reasons for exclusion, but we only mentioned the reason we thought was most important. Full details of reasons for exclusion can be found in the table of Characteristics of excluded studies.

Nineteen studies were excluded because they did not describe randomised controlled trials, for the main reason that they did not randomise their participants (Benadiva 1988; Cédrin-Durnerin 1995; Cohen 1987; Copperman 2003; Couzinet 1995; Ditkoff 1997; Forman 1991; Frydman 1986; Galera 2004; Godin 2003; Gonen 1990; Lindheim 1996; Neal 1993; Palomba 2008; Schoolcraft 1997; Surrey 1989; Tarlatzis 1993; Weisman 1989; Yokota 2006). Twenty-three studies were also no randomised controlled trials, for the main reason that their design was retrospective (al-Mizyen 2000; Bellver 2007; Bendikson 2006; Biljan 1998b; Chung 2006; Damario 1997; Dickey 2001; Duvan 2008; Frederick 2004; Gonzalez 1995; Keltz 2007; Kovacs 2001; Leondires 1999; Loutradis 2003; Min 2005; Mirkin 2003; Pados 1995; Pinkas 2008; Ramsewak 2005; Talebian 2004; Talebian 2007; Yoshida 2005; Zhao 2008). Another five studies were no randomised controlled trials, for the main reason that the women served as their own controls in previous cycles (Branigan 1998; Fanchin 2003b; Fisch 1996; Mulangi 1997; Surrey 1998). At last there were seven studies that were no randomised controlled trials because they had a single arm study design (Brodt 1993; De Ziegler 1999; Gerli 1989; Hugues 1992; Meldrum 2002; Meldrum 2008; Sanghvi 2002).

Six studies were excluded because they compared two (or more) different dosages, timings or ways of administration of the same pre-treatment (Davy 2004; Gomez 2000; Karande 2004; Lewin 2002; Mashiach 1989; Russell 1997).

Three studies were excluded because the women only received ovarian stimulation, but no embryo transfer was performed as part of an ART cycle (Anderson 1990; Letterie 2000; Steinkampf 1991).

Two studies were excluded because the women were oocyte donors (Doody 2001; Martinez 2006) and one study was excluded because the women had premature ovarian failure (Tartagni 2007).

At last, there was one study that we excluded because the oestrogen pre-treatment was not stopped before oocyte retrieval, but continued to be used as luteal phase support (Jung 2000).

Ongoing studies

One study might be eligible for inclusion in this review, but is still ongoing. We contacted the researchers, which replied that the trial is expected to be finished in June 2009 and that they are not able to share data with us until that date. More information on this trial can be found in the table of Characteristics of ongoing studies.

Risk of bias in included studies

A complete overview of classification of risk of bias domains can be found in the tables of Characteristics of included studies and in Figure 1 and Figure 2.

Allocation

All 23 included trials were claimed to be randomised, but in twelve trials the method of randomisation was not reported. Seven trials used computer generated random numbers to randomise the women (Biljan 1998a; Engmann 1999; Fanchin 2003a; Huirne 2006a; Huirne 2006b; Hwang 2004; Kolibianakis 2006). Three studies used a table of random numbers (Cédrin-Durnerin 2007; Franco Jr 2003; Shaker 1995) and one study accomplished the randomisation by tossing a coin (Ditkoff 1996).

If randomisation is not done properly, there might be a difference in baseline characteristics between the women in the treatment groups. This may influence the outcomes measured in the trial. Therefore it is important that the method of randomisation is reported. Due to the high number of included studies that did not report the method of randomisation (twelve out of 23 studies), there might be a higher risk of bias.

Ten studies were classified as 'yes' with regard to allocation concealment. Four studies used sealed envelopes to conceal the allocation (Biljan 1998a; Cédrin-Durnerin 2007; Hwang 2004; Shaker 1995). In five studies the randomisation was done by a third party (Aston 1995, hospital pharmacy and numbered bottles; Engmann 1999, clinic nurses and sealed envelopes; Fanchin 2003a, independent person; Huirne 2006b, independent person from independent monitoring company; Rombauts 2006, central remote allocation). Another study centralised the randomisation process (Ditkoff 1996).

Two studies were classified as 'no' with regard to allocation concealment, because they reported that the sequence of allocation was not concealed (Franco Jr 2003; Kolibianakis 2006). One study reported that allocation was concealed, but not how this was done (Huirne 2006a), therefore we classified this as 'unclear'.The other ten studies did not report any information about allocation concealment, and were also classified as 'unclear'.

Because nearly all outcomes of this review are not subjective, a poorly designed allocation concealment method of studies is not likely to have a big influence on these outcomes. For example, the number of live births is not likely to be influenced by the clinician if he or she knows which treatment the woman receives. However, OHS syndrome is diagnosed on clinical symptoms and so there might be a bigger risk of bias when the clinician is aware of the treatment assigned to each woman. Nevertheless, even not subjective outcomes may be influenced indirectly if allocation is not concealed.

Blinding

Three trials used blinding. One study used a placebo in the control group and reported that the study was double blind (Aston 1995). Another study used no placebo, so women could guess their treatment status, but the clinicians were blinded (Engmann 1999). The last study reported that the laboratory staff was blinded (Hwang 2004).

Nine trials reported that the study was open labelled or not blind (Cédrin-Durnerin 2007; Daly 2002; Ditkoff 1996; Fanchin 2003a; Franco Jr 2003; Huirne 2006b; Kim 2005; Kolibianakis 2006; Rombauts 2006). The other eleven studies did not report whether the women, outcome assessors or investigators were blinded.
As with allocation concealment, poor blinding is less likely to influence the objective outcomes such as live birth, but it might have a bigger influence on the diagnosis of OHS syndrome.

Incomplete outcome data

Of the 23 studies, eleven addressed incomplete outcome data (Aston 1995; Cédrin-Durnerin 1996; Ditkoff 1996; Engmann 1999; Franco Jr 2003; Huirne 2006a; Huirne 2006b; Hwang 2004; Kolibianakis 2006; Salat-Baroux 1988; Shaker 1995). In these trials the numbers and reasons for withdrawals are reported. We noticed a few imbalances in reasons for withdrawal between the study group and control group in the following studies. One study reported six withdrawals due to endometrioma, of which five were in the control group and only one in the study group (Aston 1995). Another study reported five withdrawals due to inadequate response, of which four were in the control group and only one in the study group (Salat-Baroux 1988). The third study reported three withdrawals due to risk of severe OHS syndrome in the control group and none in the study group (Hwang 2004). The last study also reported more withdrawals due to risk of OHS syndrome in the control group (n=2) than in the study group (n= 0) (Shaker 1995).
Five studies were classified as 'no', because the journal article did not report the numbers and reasons for withdrawals (in each treatment group) (Biljan 1998a; Cédrin-Durnerin 2007; Fanchin 2003a; Raoofi 2008; Rombauts 2006). We classified the other six studies as 'unclear', because there was only an abstract available that did not report any information on the numbers and reasons for withdrawal.
Incomplete outcome data can bias the results of our review, especially with regard to adverse outcomes. For example, a study might have withdrawals due to OHS syndrome that they do not report. Also imbalances in reasons for withdrawal can occur because of differences in interventions between the study group and control group. For example, when there are more withdrawals due to OHS syndrome in the control group, this can be in favour of the intervention used in the study group. The risk of bias might increase if authors do not report on this.

Selective reporting

Although we did not retrieve any of the protocols or raw data of any trial, we classified six studies as free of selective reporting, because these trials reported data on all the outcomes mentioned in the 'Methods' section of their article (Engmann 1999; Huirne 2006b; Hwang 2004; Kolibianakis 2006; Rombauts 2006; Shaker 1995).
The other seventeen studies did not report in their 'Methods' section which outcomes they were going to measure.
Because we do not know if the authors of the included studies reported all the data they retrieved in their trial, we are not able to provide a judgement about this domain.

Other potential sources of bias

Four studies were classified as 'yes', because there were no differences in baseline characteristics between the treatment groups and the number of women randomised per group was reported (Engmann 1999; Huirne 2006a; Huirne 2006b; Kolibianakis 2006).
We classified thirteen studies as 'no' with regard to other potential sources of bias. Eight studies reported no data on baseline characteristics or mentioned only one or two in the text of their articles (Cédrin-Durnerin 1996; Cédrin-Durnerin 2007; Daly 2002; Ditkoff 1996; Franco Jr 2003; Hugues 1994; Kim 2005; Obruca 2001). Two studies only reported the number of cycles in the study group and control group and did not report the number of women in each group (Biljan 1998a; Shaker 1995). Two trials did not report the number of women or cycles randomised to each group (Fanchin 2001; Raoofi 2008), and one did report the number of women analysed in each group, but not the number of women randomised to each group (Fanchin 2003a). The other six studies were classified as 'unclear', because there were not enough data on baseline characteristics available. Of these six studies, one also used a slightly different treatment protocol in both groups (Salat-Baroux 1988).
Although we classified four studies as 'yes', it is difficult to know if a study is truly free of other bias, because there are so many different potential sources of bias. It is impossible to provide a judgement about this domain based on the limited data available for us.

Effects of interventions

Combined OCP versus no pre-treatment

Live births Analysis 1.1

COCP + Antagonist versus Antagonist (five studies included) - Only one study in this subgroup reported the number of live births and found three live births in the study group (n = 21) and seven in the control group (n = 24), Peto OR 95% CI 0.43 (0.11 to 1.74); P= 0.24 (Cédrin-Durnerin 2007).
COCP + Antagonist versus Agonist (three studies included) - There was only one study that reported the number of live births in this subgroup. This study found a number of seventeen live births in

both the study (n = 91) and control group (n = 91), Peto OR 95% CI 1.00 (0.48 to 2.10); P= 1.0 (Huirne 2006a).

COCP + Antagonist versus Antagonist, low response (one study included) - This study found that there were eight live births in the study group (n = 27) and five in the control group (n = 27), Peto OR 95% CI 1.82 (0.53 to 6.25); P= 0.34 (Kim 2005).

COCP + Antagonist versus Agonist, low response (one study included) - This study found that there were eight live births in the study group (n = 27) and six in the control group (n = 28), Peto OR 95% CI 1.53 (0.46 to 5.09); P= 0.49 (Kim 2005).

Ongoing pregnancies Analysis 1.2

COCP + Antagonist versus Antagonist (five studies included) - The results of four studies, with a total of 847 women, have been pooled in this subgroup. No statistically significant difference was found ,Peto OR 0.74; 95% CI 0.53 to 1.03, P = 0.07.

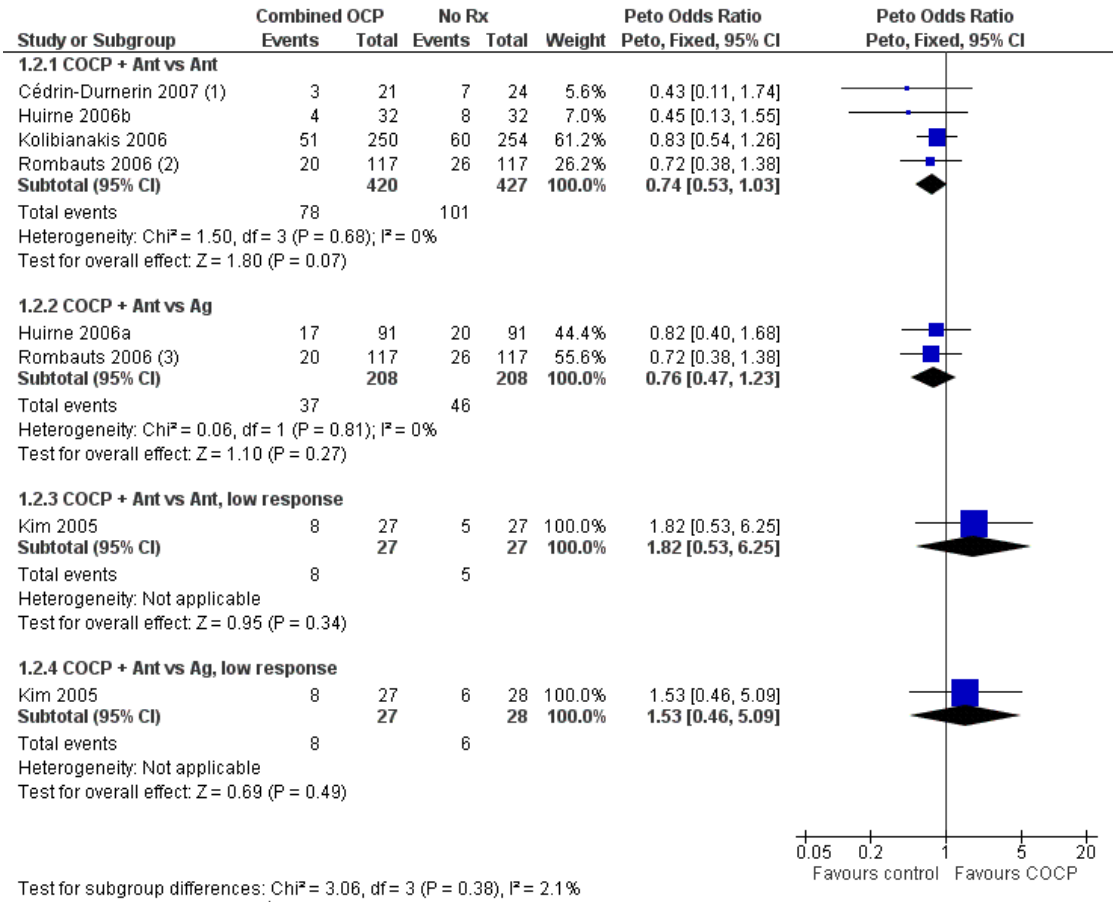
COCP + Antagonist versus Agonist (three studies included) - The results of two studies, with a total of 416 women, have been pooled in this subgroup. No statistically significant difference was found, Peto OR 0.76; 95% CI 0.47 to 1.23, P = 0.27.

COCP + Antagonist versus Antagonist, low response (one study included) -This study found an ongoing pregnancy rate of eight in the study group (n = 27) and five in the control group (n = 27), Peto OR 95% CI 0.1.82 (0.53 to 6.25); P= 0.34 (Kim 2005).

COCP + Antagonist versus Agonist, low response (one study included) - This study found an ongoing pregnancy rate of eight in the study group (n = 27) and six in the control group (n = 28), Peto OR 95% CI 1.53 (0.46 to 5.09); P= 0.49 (Kim 2005).

See Figure 3 for the graph and details of this outcome.

Figure 3. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.2 Ongoing pregnancies.



Test for subgroup differences: Chi² = 3.06, df = 3 (P = 0.38), I² = 2.1%

(1) Data obtained from Dr. Cédrin-Durnerin.

(2) Includes 2 spontaneous pregnancies in the study group and 3 in the control group.

(3) Includes 2 spontaneous pregnancies in the study group.

Clinical/ongoing pregnancies Analysis 1.3

COCP + Agonist versus Agonist (two studies included) - Both studies reported the number of clinical pregnancies, but due to a lack of data we can not pool these results. The first study reported a clinical pregnancy rate per cycle started of 37.2% in the study group and 33.3% in the control group, which comes down to 19 clinical pregnancies out of 51 cycles in the combined OCP group and 17 clinical pregnancies out of 51 cycles in the control group (Biljan 1998a). The other study reported a pregnancy rate of 9% in the study group and 11% in the control group, but did not report the number of women per group (Raoofi 2008). Both studies found that their results were not statically significant. Peto OR 1.19; 95% CI 0.53 to 2.66, P = 0.27

COCP + Antagonist versus Antagonist (five studies included) - Four RCTs have been pooled in this subgroup, with a total of 847 women. Of two of these studies we used the number of ongoing pregnancies, since no data on clinical pregnancy rate were available. There was a statistically significant difference in the rates of clinical/ongoing pregnancies with fewer clinical/ongoing pregnancies occurring in the group pre-treated with a combined OCP (Peto OR 0.69; 95% CI 0.50 to 0.96, P = 0.03). Of one study the clinical pregnancy rate per embryo transfer is known, but not the number of embryo transfers performed (Obruca 2001). The clinical pregnancy rate was 29.7% in the study group and 41.2% in the control group, this result did not reach significance according to the authors.

COCP + Antagonist versus Agonist (three studies included) - Three studies have been pooled in this subgroup, with a total of 472 women. Of one of these studies we used the number of ongoing pregnancies, since no data on clinical pregnancy rate were available. No statistically significant result was found (Peto OR 0.82; 95% CI 0.53 to 1.26, P = 0.36).

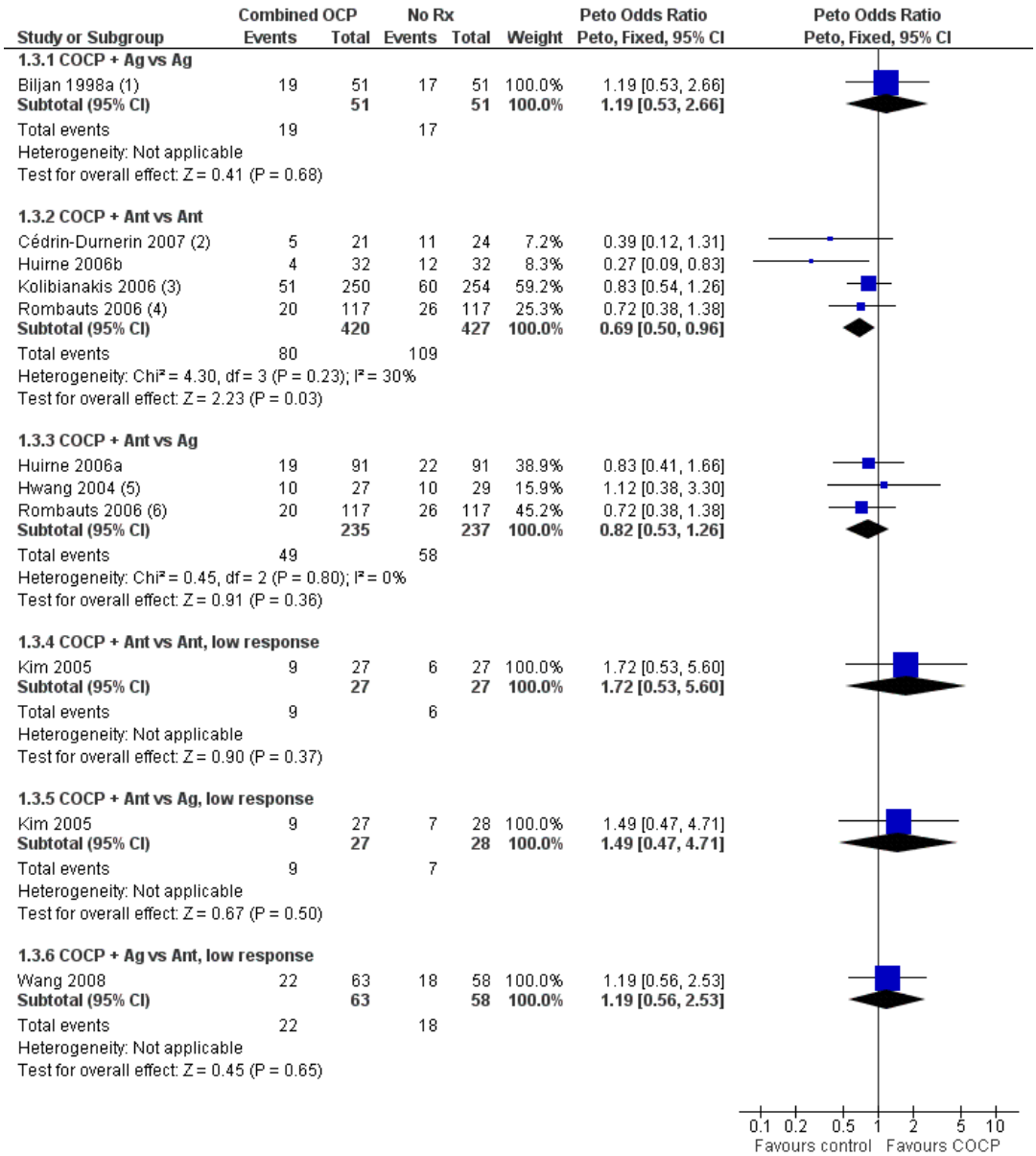
COCP + Antagonist versus Antagonist, low response (one study included) - This study found a clinical pregnancy rate of nine in the study group (n = 27) and six in the control group (n = 27), Peto OR 1.72; 95% CI 0.53 to 5.60, P = 0.37 (Kim 2005).

COCP + Antagonist versus Agonist, low response (one study included) - This study found a clinical pregnancy rate of eight in the study group (n = 27) and seven in the control group (n = 28),Peto OR 1.49; 95% CI 0.47 to 4.71, P = 0.50 (Kim 2005).

COCP + Agonist versus Antagonist, low response (one study included) - This trial found that the number of clinical pregnancies was 22 in the study group (n = 63) and 18 in the control group (n = 58), Peto OR 1.19; 95% CI 0.56 to 2.53,with a P value of 0.65 (Wang 2008).

See Figure 4 for the graph and details of this outcome.

Figure 4. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.3 Clinical/ongoing pregnancies.



(1) Numbers calculated from rates; Number of women per group unknown, only number of cycles known.
(2) Data obtained from Dr. Cédrin-Durnerin.
(3) Ongoing pregnancies.
(4) Ongoing pregnancies. Includes 2 spontaneous pregnancies in the study group and 3 in the control group.
(5) Calculated from rates.
(6) Ongoing pregnancies. Includes 2 spontaneous pregnancies in the study group.

Oocytes retrieved Analysis 1.4

COCP + Agonist versus Agonist (two studies included) - Both studies looked at the number of oocytes retrieved, but we were not able to pool or analyse these data. The first study reported a median of eleven oocytes retrieved (range seven to 19) in the study group (n = 51 cycles) and a median of ten oocytes retrieved (range 7 to 15) in the control group (n = 51 cycles) (Biljan 1998a). Because of the statistical method used in this study, we can not analyse these data. The other study reported a mean number of oocytes retrieved of 5.0 (± 2.8) in the study group and 5.4 (± 5.7) in the control group (Raoofi 2008). This study did not report the number of women or cycles in each treatment group, and therefore we can not use these data in our analysis.

COCP + Antagonist versus Antagonist (five studies included) - Results of all five included trials have been pooled, with a total of 891 women. No statistically significant difference was found for this outcome (MD 0.23; 95% CI -0.55 to 1.01, P = 0.56). However, we found a substantial amount of heterogeneity; the I^2 statistic is 64%. No obvious reasons were identified for the heterogeneity in this comparison. An overview of characteristics of the studies for this subgroup are reported in Table 1.

COCP + Antagonist versus Agonist (three studies included) - The results of three RCTs have been pooled in this subgroup, with a total of 440 women. No statistically significant result was found (MD -0.01; 95% CI -1.54 to 1.53, P = 0.99).

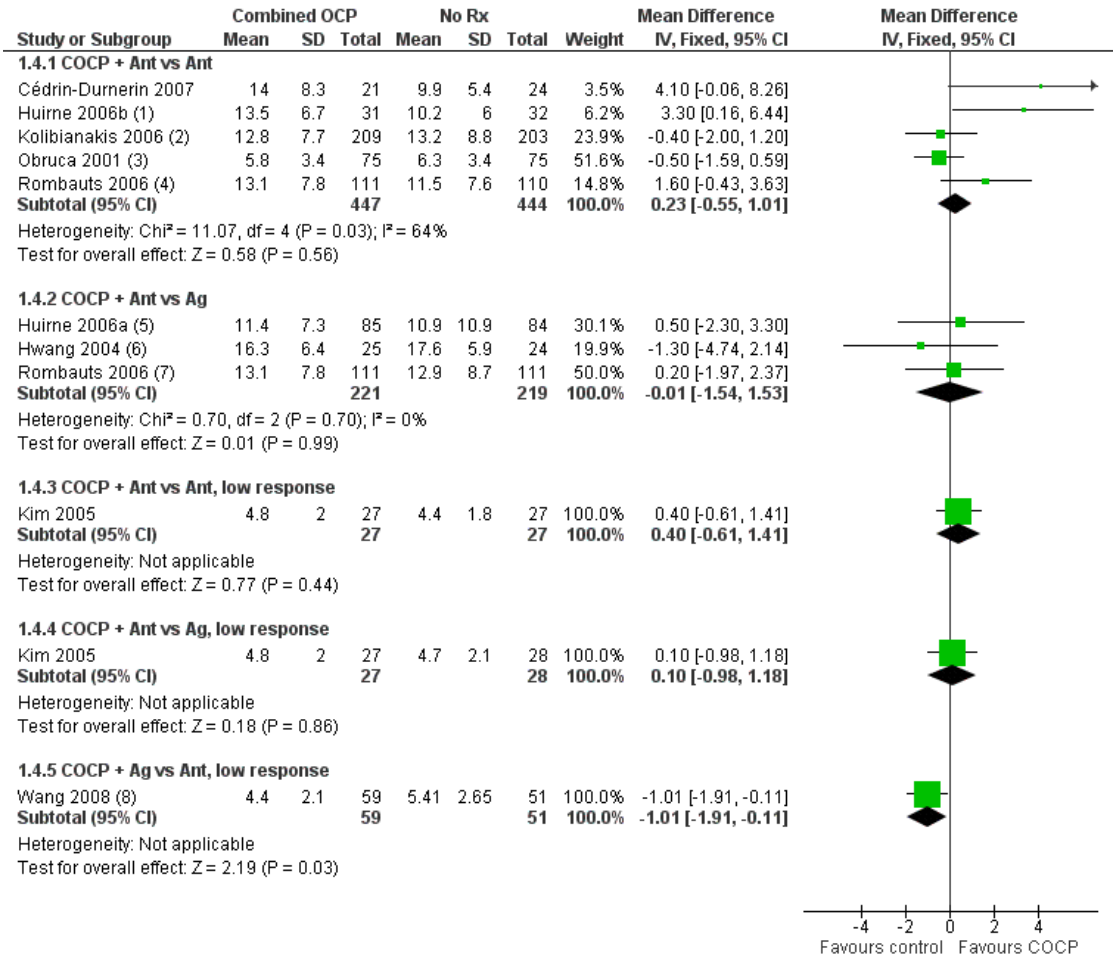
COCP + Antagonist versus Antagonist, low response (one study included) - This study found a mean number of 4.8 (± 2.0) oocytes retrieved in the study group (n=27) and a mean number of 4.4 (± 1.8) oocytes retrieved in the control group (n = 27), Peto OR 0.27; 95% CI -0.61 to 1.41, P = 0.44 (Kim 2005).

COCP + Antagonist versus Agonist, low response (one study included) - This study found a mean number of 4.8 (± 2.0) oocytes retrieved in the study group (n = 27) and a mean number of 4.7 (± 2.1) oocytes retrieved in the control group (n = 28),Peto OR 0.10; 95% CI -0.98 to 1.18, P = 0.86 (Kim 2005).

COCP + Agonist versus Antagonist, low response (one study included) - This study found a mean number of 4.40 (± 2.1) oocytes retrieved in the study group (n = 59) and 5.41 (± 2.65) in the control group (n = 51), Peto OR -1.01; 95% CI -1.91 to 0.11, P =0.03 (Wang 2008).

See Figure 5 for the graph and details of this outcome.

Figure 5. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.4 Oocytes retrieved.



(1) No ITT in COCP group.
(2) No ITT. 'Cumulus oocyte complexes'.
(3) Unsure about ITT.
(4) No ITT.
(5) No ITT.
(6) No ITT.
(7) No ITT.
(8) No ITT.

Days of gonadotrophin treatment Analysis 1.5

COCP + Agonist versus Agonist (two studies included) - Only one study reported on the number of days of gonadotrophin treatment (Biljan 1998a). This study found a median of ten days (range 9 to 11) in the study group (n = 51 cycles) and a median of twelve days (range 11 to 12) in the control group (n = 51 cycles). Because of the statistical method used in this study, we can not analyse these data.

COCP + Antagonist versus Antagonist (five studies included) - Three RCTs have been pooled in this subgroup for this outcome, with a total of 689 women. There was a significant difference, with fewer days of gonadotrophin treatment in the group that did not receive pre-treatment with a combined OCP (MD 1.44; 95% CI 1.15 to 1.72, P < 0.00001). Heterogeneity in this meta-analysis was high, with an I^2 statistic of 95%. A possible explanation for the high heterogeneity might be that Kolibianakis 2006 uses a shorter duration of pre-treatment than the other studies. We did a sensitivity analysis to explore this heterogeneity and found that removing Kolibianakis 2006 from this meta-analysis reduced heterogeneity to 22%. This did not change the results substantially. An overview of characteristics of the studies for this subgroup are reported in Table 1.

COCP + Antagonist versus Agonist (three studies included) - Also, three RCTs have been pooled in this subgroup, with a total of 434 women. There was a significant difference in this outcome, with fewer days of gonadotrophin treatment in the group that did not receive pre-treatment with a combined OCP (MD 0.51; 95% CI 0.17 to 0.84, P = 0.003). The heterogeneity was high, with an I^2 statistic of 92%. The only substantial difference that we noticed was that Rombauts 2006 used a different type of GnRH antagonist and agonist and had a higher starting dose of gonadotrophins than the other studies. We did a sensitivity analysis on the outcome number of days of gonadotrophin therapy and found that removing Rombauts 2006 from this meta-analysis reduced heterogeneity to 9%. An overview of characteristics of the studies for this subgroup are reported in Table 2.

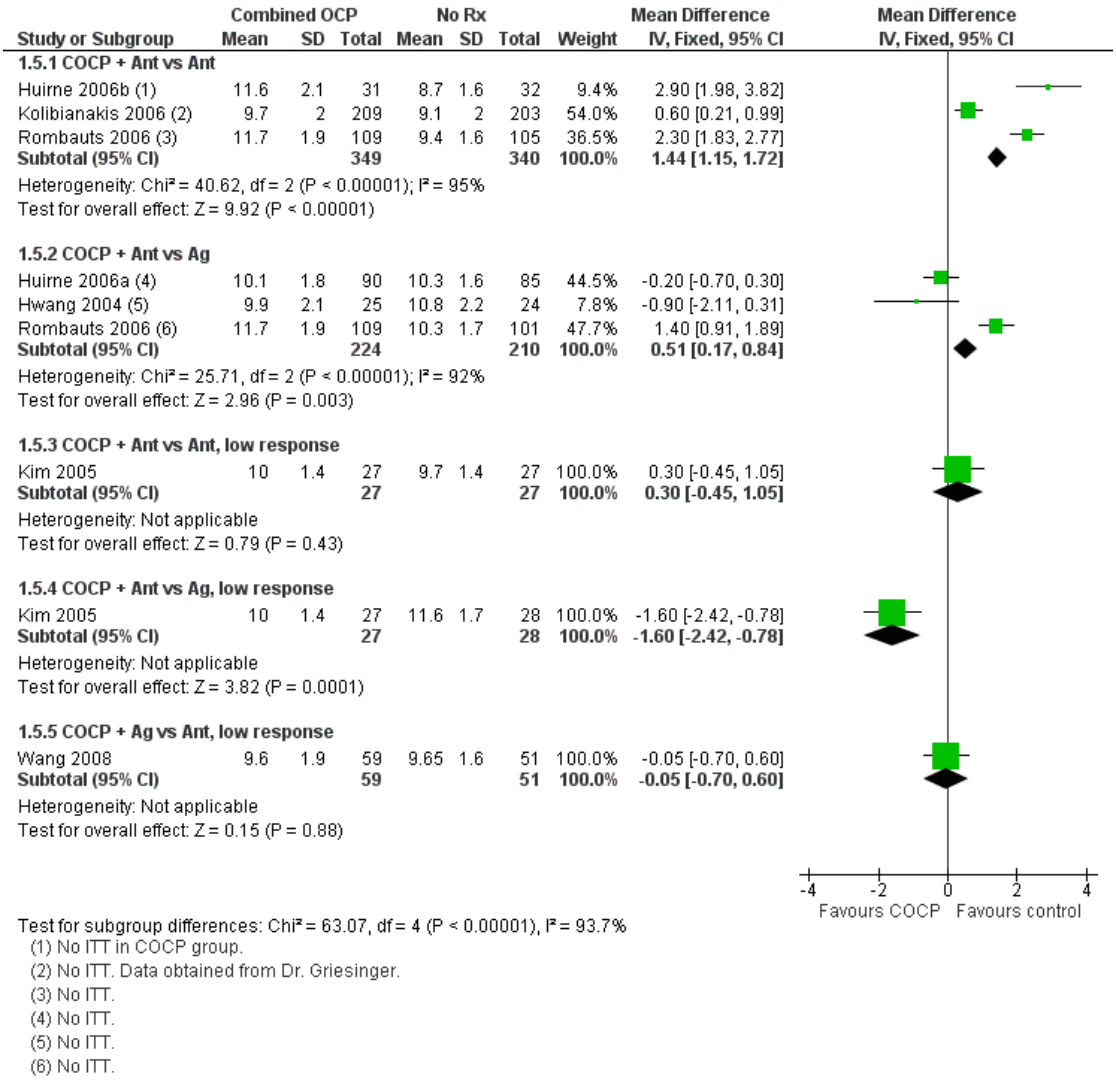
COCP + Antagonist versus Antagonist, low response (one study included) - This study found a mean number of 10.0 (± 1.4) days of gonadotrophin treatment in the study group (n = 27) and a mean number of 9.7 (± 1.4) days in the control group (n = 27), MD 0.30; 95% CI -0.45 to 1.05, P = 0.43 (Kim 2005).

COCP + Antagonist versus Agonist, low response - This study found a mean number of 10.0 (± 1.4) days of gonadotrophin treatment in the study group (n = 27) and a mean number of 11.6 (± 1.7) days in the control group (n = 28), MD -1.60; 95% CI -2.42 to 0.78, P = 0.0001 (Kim 2005) .

COCP + Agonist versus Antagonist, low response (one study included) - This study found that the mean length of gonadotrophin therapy was 9.60 (± 1.90) days in the study group (n = 59) and 9.65 (± 1.60) in the control group (n = 51), MD -0.50; 95% CI -0.70 to 0.60, P = 0.88 (Wang 2008).

See Figure 6 for the graph and details of this outcome.

Figure 6. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.5 Days of gonadotrophin treatment.



Amount of gonadotrophins administered Analysis 1.6

COCP + Antagonist versus Antagonist (five studies included) - The results of four studies have been pooled in this subgroup and for this outcome, with a total of 734 women. There was a statistically significant difference, with fewer gonadotrophins administered in the group that did not receive pre-treatment with a combined OCP (MD 231.14; 95% CI 161.50 to 300.78, P < 0.00001). Heterogeneity in this meta-analysis was high with an I^2 statistic of 93%. We did a sensitivity analysis to explore this heterogeneity and found that a possible explanation could be that Kolibianakis 2006 uses a shorter duration of pre-treatment than the other studies. By removing Kolibianakis 2006 from the meta-analysis heterogeneity was reduced to 43%. This did not change the results substantially. An overview of characteristics of the studies for this subgroup are reported in Table 1.

COCP + Antagonist versus Agonist (three studies included) - Two RCTs have been pooled for this outcome, with a total of 385 women. There was a significant difference favouring the group that did not receive pre-treatment with a combined OCP (MD 209.52; 95% CI 61.16 to 357.87, P = 0.006). The heterogeneity in this

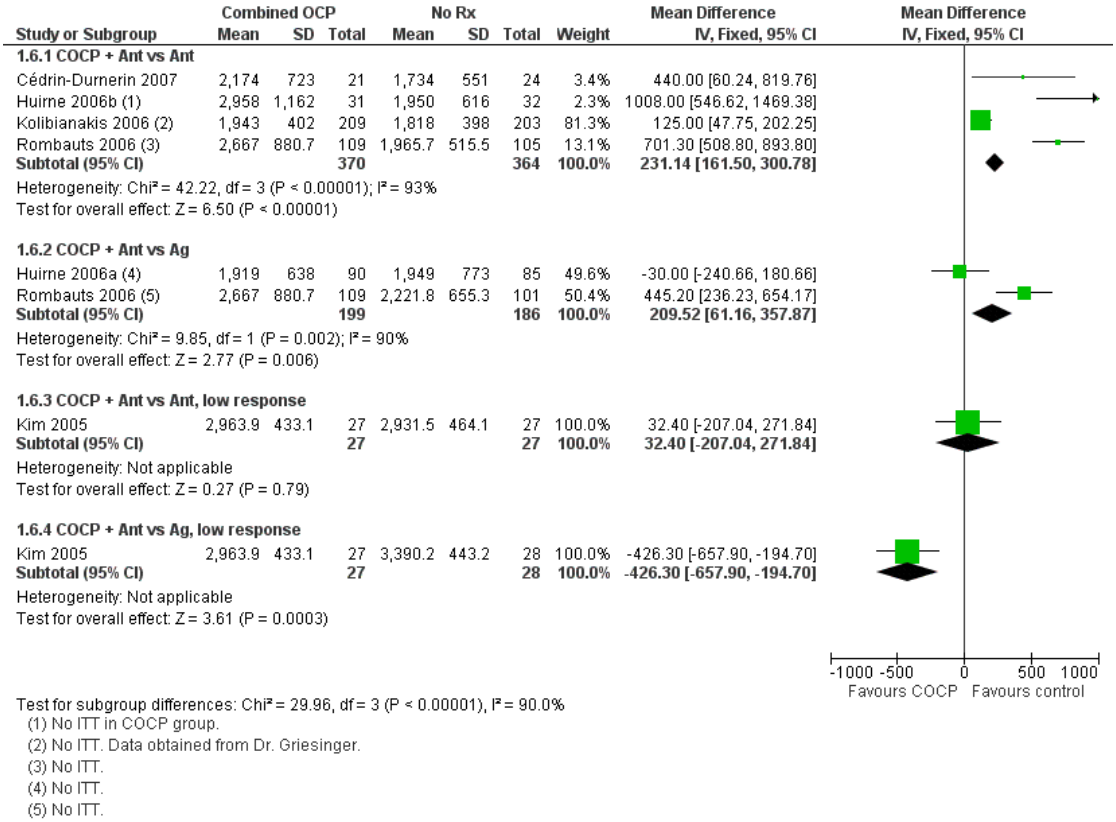
subgroup was also high, with an I^2 statistic of 90%. We were not able to perform a sensitivity analysis, because there were only two studies that reported the amount of gonadotrophins administered in this subgroup. An overview of characteristics of these two studies are reported in Table 2.

COCP + Antagonist versus Antagonist, low response (one study included) - This study reported a mean amount of 2963.9 (± 433.1) IU gonadotrophins administered in the study group (n = 27) and a mean of 2931.5 (± 464.1) IU in the control group (n = 27), MD 32.40; 95% CI -207.04 to 271.84, P = 0.79 (Kim 2005).

COCP + Antagonist versus Agonist, low response (one study included) - This study reported a mean amount of 2963.9 (± 433.1) IU gonadotrophins administered in the study group (n = 27) and a mean of 3390.2 (± 443.2) IU in the control group (n = 28), MD -426.30; 95% CI -657.90 to -194.70, P = 0.0003, which makes this difference statistically significant (Kim 2005).

See Figure 7 for the graph and details of this outcome.

Figure 7. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.6 Amount of gonadotrophins administered.



Pregnancy losses Analysis 1.7

COCP + Antagonist versus Antagonist (five studies included) - The results of four trials have been pooled in this subgroup, with a total of 847 women. The number of pregnancy losses did not differ statistically significantly between groups (Peto OR 1.26; 95% CI 0.76 to 2.12, P = 0.37).

COCP + Antagonist versus Agonist (three studies included) - The results of three trials have been pooled, with a total of 472 women. There was no statistically significant result (Peto OR 0.52; 95% CI 0.24 to 1.10, P = 0.09).

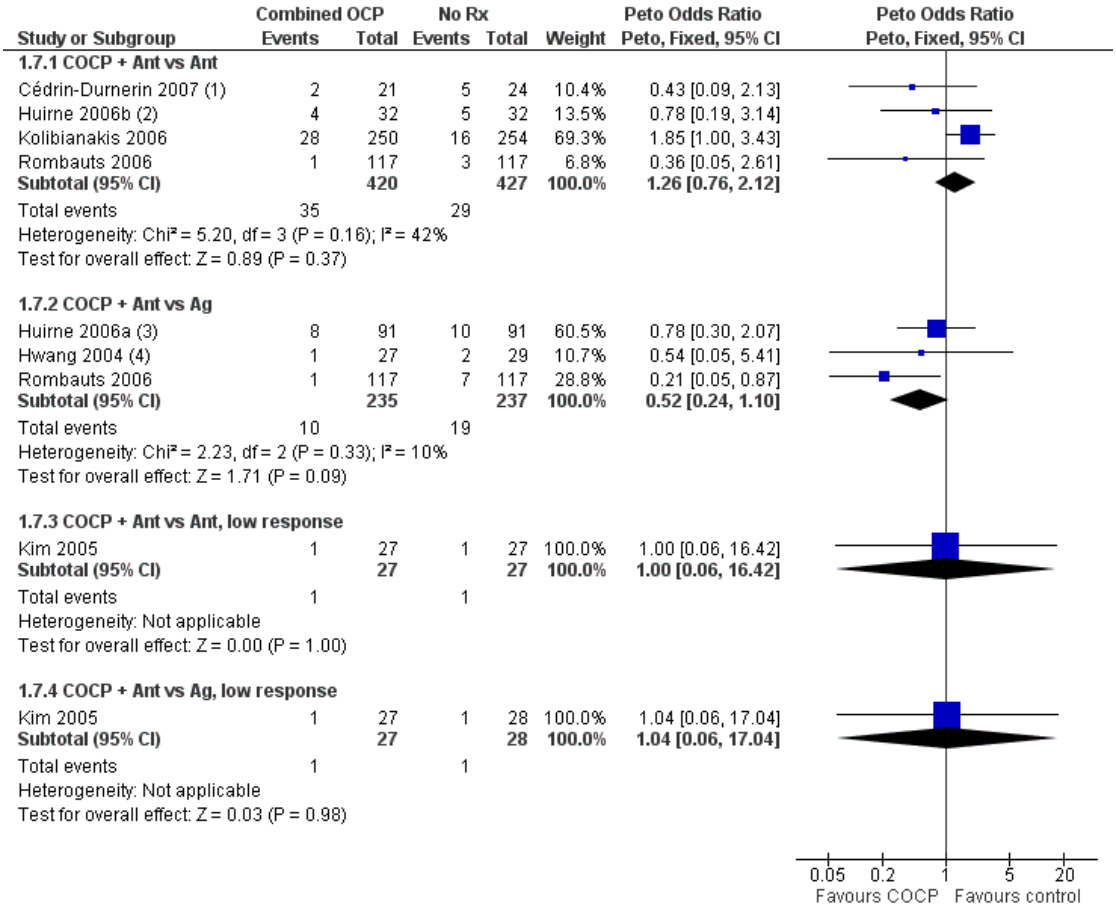
COCP + Antagonist versus Antagonist, low response (one study in-

cluded) - This study found that there was one pregnancy loss in both the study (n = 27) and the control group (n = 27)OR 1.0; 95% CI 0.06 to 16.42 (Kim 2005).

COCP + Antagonist versus Agonist, low response (one study included) -This study found that there was one pregnancy loss in both the study (n = 27) and the control group (n = 28), OR 1.04; 95% CI 0.06 to 17.04, P =0.98 (Kim 2005).

See Figure 8 for the graph and details of this outcome.

Figure 8. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.7 Pregnancy losses.



(1) Calculated from the number of clinical pregnancies minus the number of live births.
(2) Calculated from the number of positive pregnancy tests minus the number of ongoing pregnancies.
(3) Calculated from the number of positive pregnancy tests minus the number of live births.
(4) Calculated from rates.

Ovarian cyst formation Analysis 1.8

COCP + Agonist versus Agonist (two studies included) - Two studies reported on cyst formation, but results could not be pooled

or analysed because the number of women in each study or control group is unknown. The first study found that the number of women in which cyst formation occurred was none in the study group (n = 51 cycles) and 27 in the control group (n = 51 cycles) (Biljan 1998a). This result was statistically significant according to the authors OR 0.O7; 95% CI 0.03 to 0.16, (P < 0.0001). Raoofi 2008 reported no women with cyst formation in both the study group and the control group.

COCP + Antagonist versus Antagonist (five studies included) - In this subgroup, the number of women with ovarian cysts was reported by one study, that found two women with ovarian cysts in the study group (n = 32) and four women in the control group (n = 32), OR 0.48; 95% CI 0.09 to 2.57, P = 0.39 (Huirne 2006b).

Multiple pregnancies Analysis 1.9

COCP + Antagonist versus Antagonist (five studies included) - Only one study in this subgroup reported this outcome and found two multiple pregnancies in the study group (n = 21) and one in the control group (n = 24), withOR 2.32; 95% CI 0.23 to 23.65 P value of 0.48 (Cédrin-Durnerin 2007).

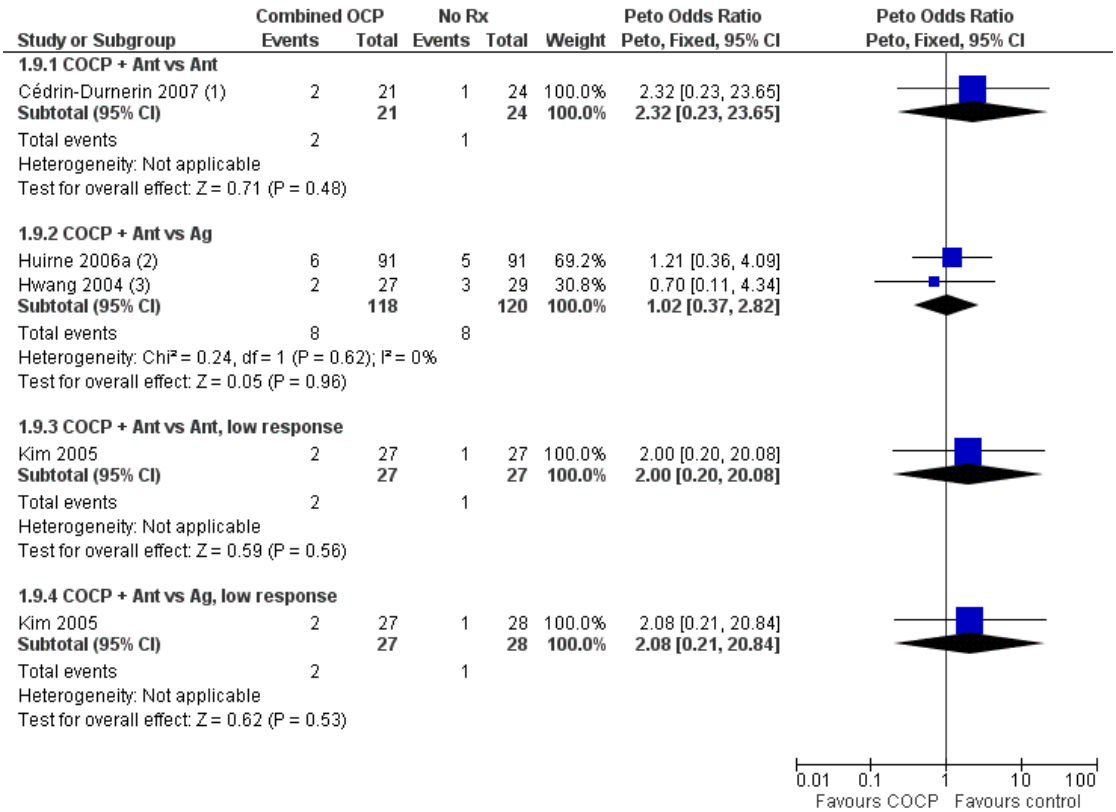
COCP + Antagonist versus Agonist (three studies included) - Two of the trials included in this subgroup reported on this outcome, with a total of 238 women. The pooling of these results showed no statistically significant difference between treatment groups (Peto OR 1.02; 95% CI 0.37 to 2.82, P = 0.96).

COCP + Antagonist versus Antagonist, low response (one study included) - The only study in this subgroup (Kim 2005) found two multiple pregnancies in the study group (n = 27) and one in the control group (n = 27), OR 2.00; 95% CI 0.20 to 20.08 ,P= 0.56.

CP + Antagonist versus Agonist, low response (one study included) - The only study in this subgroup (Kim 2005) found two multiple pregnancies in the study group (n = 27) and one in the control group (n = 28), OR 2.08; 95% CI 0.21 to 20.84,P= 0.53.

See Figure 9 for the graph and details of this outcome.

Figure 9. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.9 Multiple pregnancies.

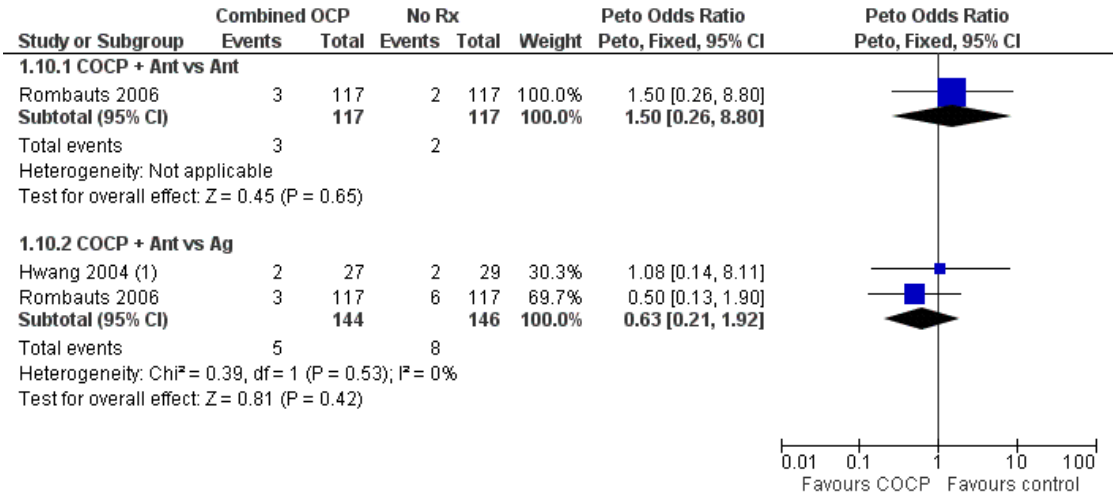


(1) Data obtained from Dr. Griesinger.
(2) 'Multiple clinical pregnancies'.
(3) Data obtained from text. In the study group 2 ongoing. In the control group 1 live birth and 2 ongoing.

OHS syndrome Analysis 1.10

COCP + Antagonist versus Antagonist (five studies included) - Only one study in this subgroup reported on this outcome and found three women with OHS syndrome in the study group (n = 117) and two women with OHS syndrome in the control group (n = 117), OR 1.50; 95% CI 0.26 to 8.80, P = 0.65 (Rombauts 2006).
COCP + Antagonist versus Agonist (three studies included) - Two studies, with a total of 290 women, reported on this outcome. The pooling showed no statistically significant difference between treatment groups (Peto OR 0.63; 95% CI 0.21 to 1.92, P = 0.42).
See Figure 10 for the graph and details of this outcome.

Figure 10. Forest plot of comparison: 1 Combined OCP versus no Rx, outcome: 1.10 OHS syndrome.



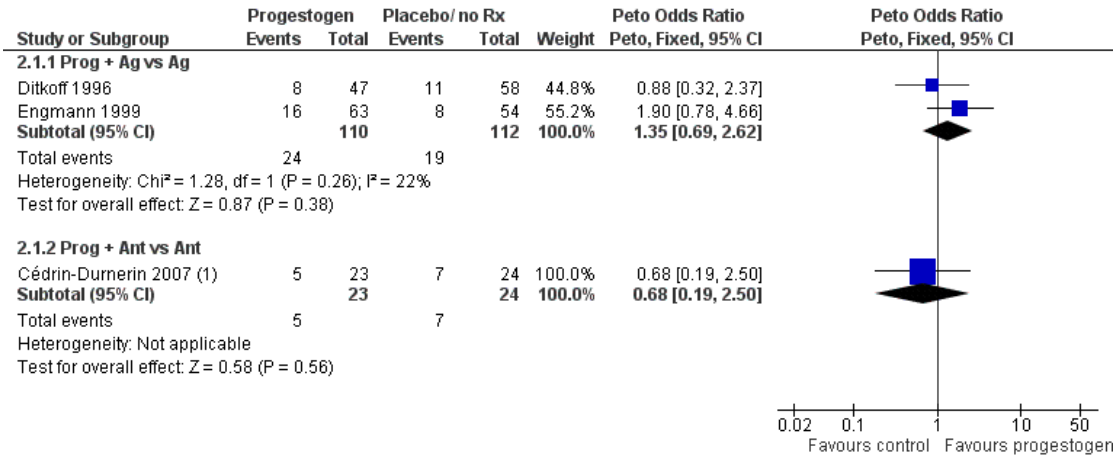
(1) Calculated from rates.

Progestogen versus placebo or no pre-treatment

Live births Analysis 2.1

Progestogen + Agonist versus Agonist (six studies included) - Two of the studies in this subgroup reported on the live birth rate, with a total of 222 women. There was no statistically significant difference found between the study group and the control group (Peto OR 1.35; 95% CI 0.69 to 2.62, P = 0.38).
Progestogen + Antagonist versus Antagonist (one study included) - Only one study could be included in this subgroup and this study found a number of five live births in the study group (n = 23) and seven live births in the control group (n = 24), Peto OR 0.68; 95% CI 0.19 to 2.50, P = 0.56 (Cédrin-Durnerin 2007).
See Figure 11 for the graph and details of this outcome.

Figure 11. Forest plot of comparison: 2 Progestogen versus placebo/ no Rx, outcome: 2.1 Live births.



(1) Data obtained from Dr. Griesinger.

Ongoing pregnancies Analysis 2.2

Progestogen + Agonist versus Agonist (six studies included) - Only one study in this subgroup reported ongoing pregnancy rate (Ditkoff 1996). The number of ongoing pregnancies was found to be eleven in the study group (n = 47) and twelve in the control group (n = 58), Peto OR 1.17; 95% CI 0.46 to 2.95, P = 0.74.

Progestogen + Antagonist versus Antagonist (one study included) - The only study in this subgroup reported five ongoing pregnancies in the study group (n = 23) and seven in the control group (n = 24), Peto OR 0.68; 95% CI 0.19 to 2.50, P = 0.56 (Cédrin-Durnerin 2007).

Progestogen + Gonadotrophins versus Gonadotrophins (one study included) - This study found two ongoing pregnancies in the study group (n = 21) and three in the control group (n = 21), Peto OR 0.64; 95% CI 0.10 to 4.06, P = 0.64 (Salat-Baroux 1988).

Clinical/ongoing pregnancies Analysis 2.3

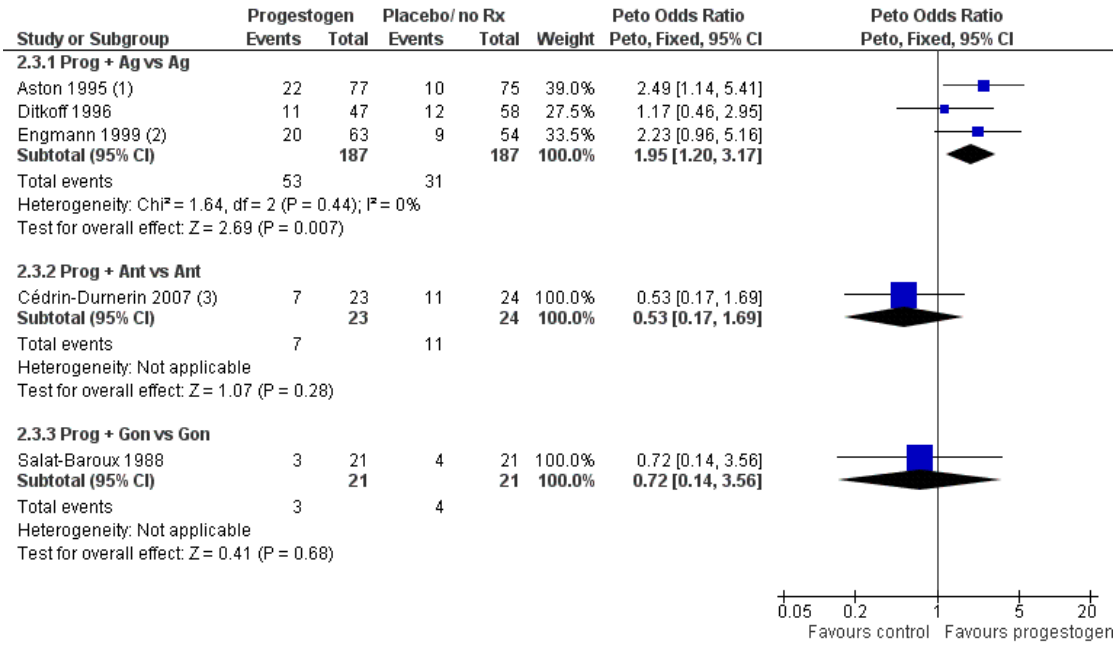
Progestogen + Agonist versus Agonist (six studies included) - Results of three of the studies in this subgroup could be pooled with a total of 374 women. Of one of these studies we used the number of positive pregnancy tests, because no data on clinical pregnancy rate were available. A statistically significant result was found, with more clinical pregnancies obtained in the group pre-treated with a progestogen (Peto OR 1.95; 95% CI 1.20 to 3.17, P = 0.007). Another study in this subgroup reported on this outcome (Shaker 1995), but because only the number of cycles per group was known and not the number of women, data have not been pooled. In this study the number of clinical pregnancies was seven in the study group (n = 22 cycles) and four in the control group (n = 29 cycles). This result was not statistically significant according to the authors.

Progestogen + Antagonist versus Antagonist (one study included) - The only study in this subgroup (Cédrin-Durnerin 2007) found a number of seven clinical pregnancies in the study group (n = 23) and twelve in the control group (n = 24), Peto OR 0.53; 95% CI 0.17to 1.69, P = 0.28.

Progestogen + Gonadotrophins versus Gonadotrophins (one study included) - The only study in this subgroup (Salat-Baroux 1988) found a number of three clinical pregnancies in the study group (n = 21) and four in the control group (n = 21), Peto OR 0.72; 95% CI 0.14 to 3.56, P = 0.68.

See Figure 12 for the graph and details of this outcome.

Figure 12. Forest plot of comparison: 2 Progestogen versus placebo/ no Rx, outcome: 2.3 Clinical pregnancies.



(1) Numbers calculated from rates.
(2) Positive pregnancy test.
(3) Data obtained from Dr. Cédrin-Durnerin.

Oocytes retrieved Analysis 2.4

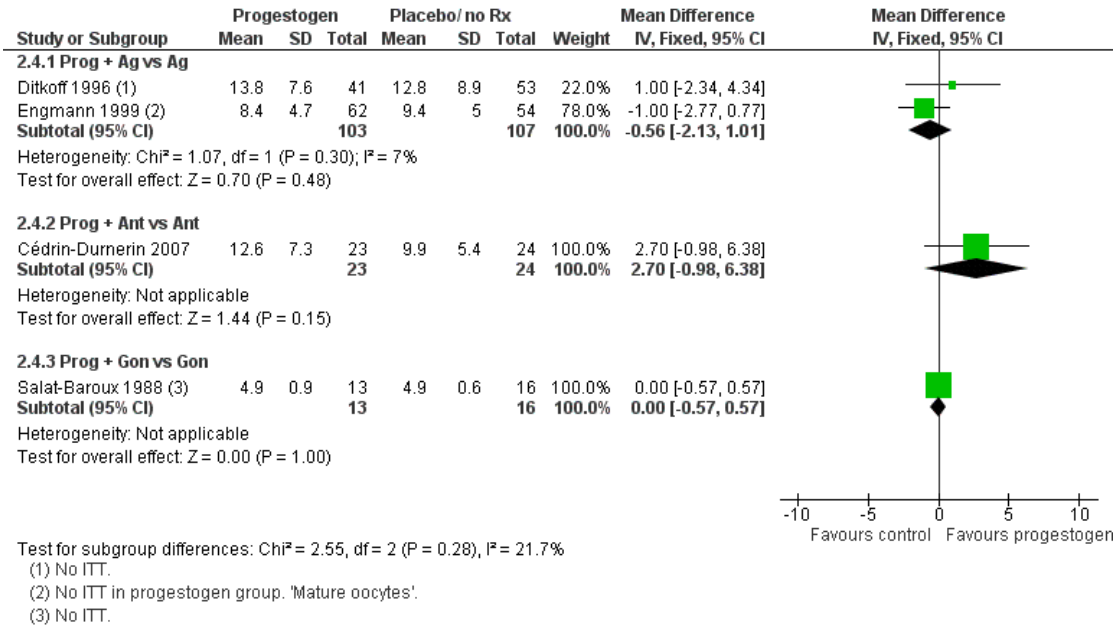
Progestogen + Agonist versus Agonist (six studies included) - Results of two of the studies in this subgroup have been pooled, with a total of 210 women. No statistically significant result was found (MD -0.56; 95% CI -2.13 to 1.01, P = 0.48) There was one other study in this subgroup that reported the mean number of oocytes retrieved, but because this was analysed per cycle (in stead of per woman randomised), we have not pooled the data of this study (Shaker 1995). The mean number of oocytes retrieved was 9.82 (± 1.09) in the study group (n = 22) and 9.1 (± 1.09) in the control group (n = 29) and this result was not statistically significant according to the authors, but no P values were given.

Progestogen + Antagonist versus Antagonist (one study included) - Only one study could be included in this subgroup (Cédrin-Durnerin 2007). This study found that the mean number of oocytes retrieved was 12.6 (± 7.3) in the study group (n = 23) and 9.9 (± 5.4) in the control group (n = 24), Peto OR 2.70; 95% CI -0.98 to 6.38, P = 0.15.

Progestogen + Gonadotrophins versus Gonadotrophins (one study included) - The only study in this subgroup (Salat-Baroux 1988) found that the mean number of oocytes retrieved was 4.9 (± 0.9) in the study group (n = 13) and 4.9 (± 0.6) in the control group (n = 16), Peto OR 0.00; 95% CI -0.57 to 0.57, P = 1.00.

See Figure 13 for the graph and details of this outcome.

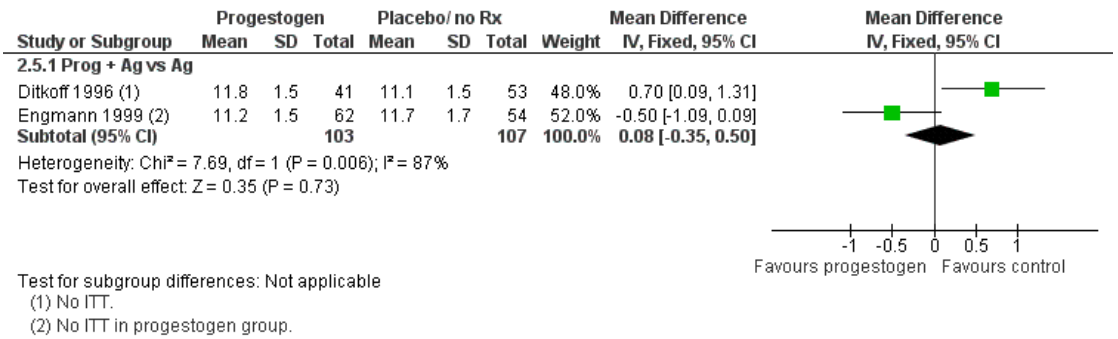
Figure 13. Forest plot of comparison: 2 Progestogen versus placebo/ no Rx, outcome: 2.4 Oocytes retrieved.



Days of gonadotrophin treatment Analysis 2.5

Progestogen + Agonist versus Agonist (six studies included) - Results of two RCTs in this subgroup have been pooled, with a total of 210 women. No statistically significant difference was found (MD 0.08; 95% CI -0.35 to 0.50, P = 0.73) . Another study in this subgroup only reported the mean number of days of gonadotrophin therapy per cycle (in stead of per woman randomised) and found that this was 11.8 (± 0.51) in the study group (n = 22) and 11.48 (± 0.37) in the control group (n = 29) (Shaker 1995). This result did not reach statistical significance according to the authors.
See Figure 14 for the graph and details of this outcome.

Figure 14. Forest plot of comparison: 2 Progestogen versus placebo/ no Rx, outcome: 2.5 Days of gonadotrophin treatment.



Amount of gonadotrophins administered Analysis 2.6

Progestogen + Antagonist versus Antagonist (one study included) - Only one trial reported on this outcome (Cédrin-Durnerin 2007) and found that the mean amount of gonadotrophins administered was 2,010 (± 670) IU in the study group (n = 23) and 1,734 (± 551) IU in the control group (n = 24), Peto OR 2.76.00; 95% CI 0.-75.53 to 672.53, P = 0.12.

Pregnancy losses Analysis 2.7

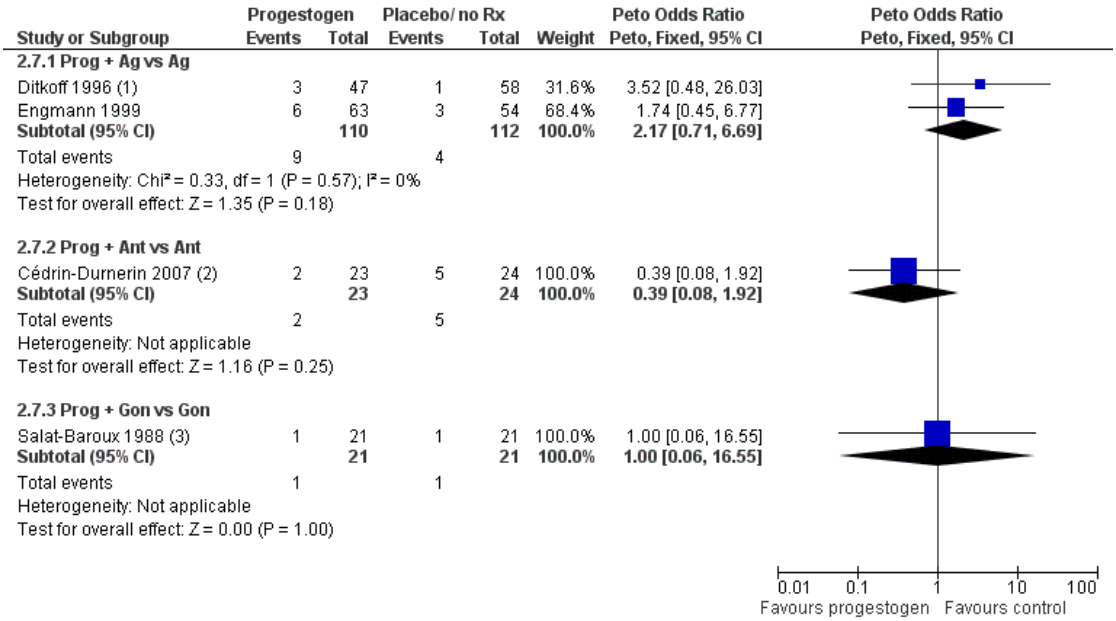
Progestogen + Agonist versus Agonist (six studies included) - Results of two trials of this subgroup have been pooled, with a total of 222 women. There was no statistically significant difference found between the study group and the control group (Peto OR 2.17; 95% CI 0.71 to 6.69, P = 0.18).

Progestogen + Antagonist versus Antagonist (one study included) - The only study in this subgroup (Cédrin-Durnerin 2007) did not report on the number of pregnancy losses, but we calculated this number by subtracting the number of live births from the number of clinical pregnancies. Through this we found two pregnancy losses in the study group (n = 23) and five in the control group (n = 24), Peto OR 0.39; 95% CI 0.08 to 1.92, P = 0.25.

Progestogen + Gonadotrophins versus Gonadotrophins (one study included) - The only trial included in this subgroup found one pregnancy loss in each treatment group (n = 21 in each group), but we are not sure if the follow up was long enough to detect all pregnancy losses (Salat-Baroux 1988) .

See Figure 15 for the graph and details of this outcome.

Figure 15. Forest plot of comparison: 2 Progestogen versus placebo/ no Rx, outcome: 2.7 Pregnancy losses.

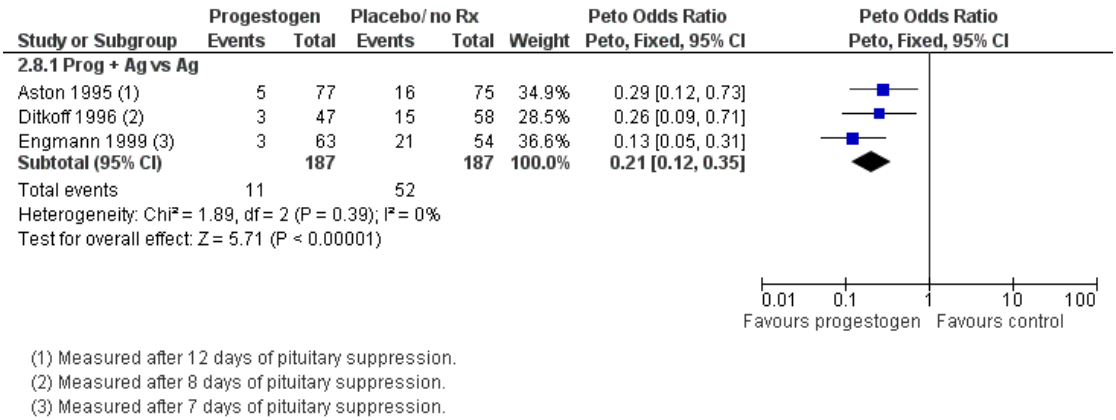


(1) Calculated from the number of clinical pregnancies minus the number of live births.
(2) Calculated from the number of clinical pregnancies minus the number of live births.
(3) Data obtained from text, not sure whether follow up was long enough.

Ovarian cyst formation Analysis 2.8

Progestogen + Agonist versus Agonist (six studies included) - Three of the studies in this subgroup, with a total of 374 women, reported on this outcome and data have been pooled. We found that there was a statistically significant difference, with less ovarian cyst formation in the group pre-treated with a progestogen (Peto OR 0.21; 95% CI 0.12 to 0.35, P < 0.00001).
See Figure 16 for the graph and details of this outcome.

Figure 16. Forest plot of comparison: 2 Progestogen versus placebo/ no Rx, outcome: 2.8 Ovarian cyst formation.



(1) Measured after 12 days of pituitary suppression.
(2) Measured after 8 days of pituitary suppression.
(3) Measured after 7 days of pituitary suppression.

Multiple pregnancies Analysis 2.9

Progestogen + Antagonist versus Antagonist (one study included) - The only trial included in this subgroup found one multiple pregnancy in both the study group (n = 23) and control group (n = 24), Peto OR 1.04; 95% CI 0.06 to 17.23, P = 0.98 (Cédrin-Durnerin 2007).

OHS syndrome

None of the studies in which the study group was administered a progestogen pre-treatment reported on the number of women with OHS syndrome.

Estrogen versus no pre-treatment

Live births Analysis 3.1

Estrogen + Antagonist versus Antagonist (two studies included) - Only one study in this subgroup reported on this outcome and found three live births in the study group (n = 25) and seven in the control group (n = 24), Peto OR 0.36; 95% CI 0.0.09 to 1.41, P = 0.14 (Cédrin-Durnerin 2007).
Estrogen + Antagonist versus Agonist (one study included) - Only one study was included in this subgroup, and this study found five live births in the study group (n = 16) and two in the control group (n = 6), Peto OR 0.91; 95% CI 0.13 to 6.53, P = 0.93 (Franco Jr 2003).

Ongoing pregnancies Analysis 3.2

Estrogen + Antagonist versus Antagonist (two studies included) - Only one study in this subgroup reported on this outcome and found three ongoing pregnancies in the study group (n = 25) and seven in the control group (n = 24), Peto OR 0.36; 95% CI 0.09 to 1.41 P = 0.14 (Cédrin-Durnerin 2007).
Estrogen + Antagonist versus Agonist (one study included) - This

study found five ongoing pregnancies in the study group (n = 16) and two in the control group (n = 6), Peto OR 0.91; 95% CI 0.13 to 6.53, P = 0.93 (Franco Jr 2003).

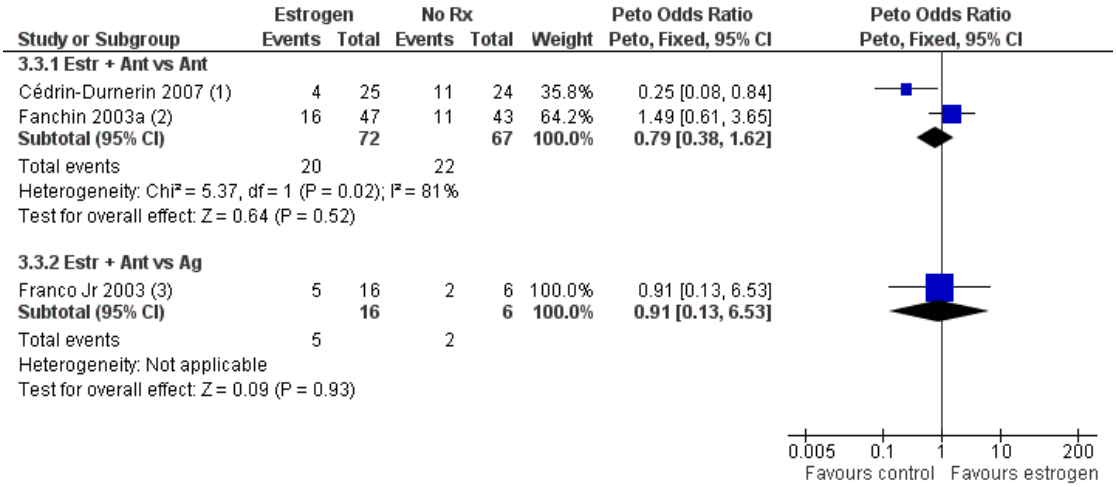
Clinical/ongoing pregnancies Analysis 3.3

Estrogen + Antagonist versus Antagonist (two studies included) - Both studies in this subgroup, with a total 139 women, reported on the number of clinical pregnancies and data have been pooled. No statistically significant difference was found (Peto OR 0.79; 95% CI 0.38 to 1.62, P = 0.52).

Estrogen + Antagonist versus Agonist (one study included) - The only study in this subgroup found five clinical pregnancies in the study group (n = 16) and two in the control group (n = 6), Peto OR 1.35; 95% CI 0.13 to 6.53, P = 0.93 (Franco Jr 2003).

See Figure 17 for the graph and details of this outcome.

Figure 17. Forest plot of comparison: 3 Estrogen versus no Rx, outcome: 3.3 Clinical pregnancies.



(1) Data obtained from Dr. Cédrin-Durnerin.
(2) No ITT. Calculated from rates.
(3) Includes 2 spontaneous pregnancies in the study group.

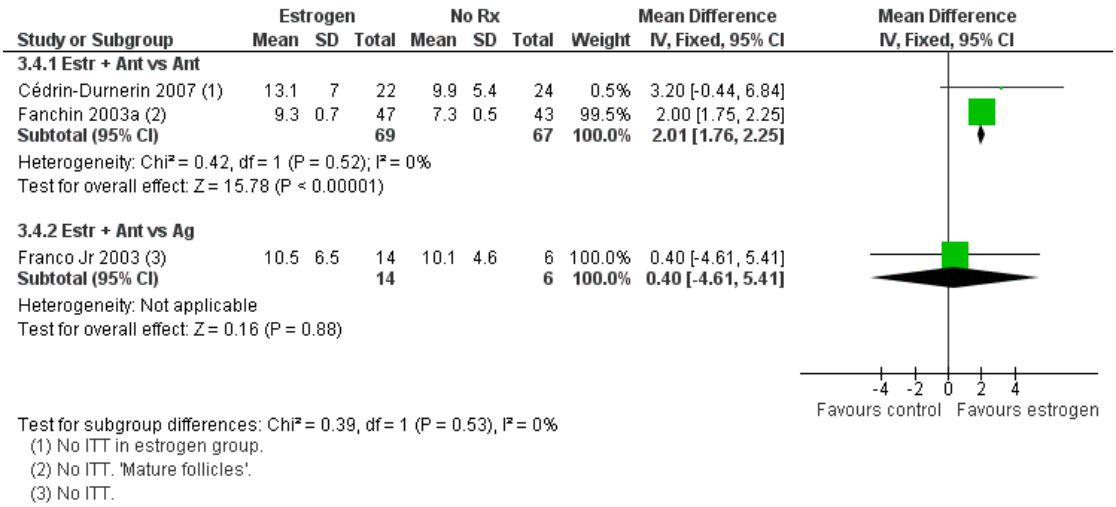
Oocytes retrieved Analysis 3.4

Estrogen + Antagonist versus Antagonist (two studies included) - Both studies in this subgroup, with a total of 136 women, reported on the number of oocytes retrieved and data have been pooled. A statistically significant difference was found, with more oocytes retrieved in the group pre-treated with oestrogen (MD 2.01; 95% CI 1.76 to 2.25, P < 0.00001).

Estrogen + Antagonist versus Agonist (one study included) - This study found a mean number of oocytes retrieved of 10.5 (± 6.5) in the study group (n = 14) and of 10.1 (± 4.6) in the control group (n = 6), Peto OR -2.50; 95% CI -4.61 to 5.41, P = 0.88 (Franco Jr 2003).

See Figure 18 for the graph and details of this outcome.

Figure 18. Forest plot of comparison: 3 Estrogen versus no Rx, outcome: 3.4 Oocytes retrieved.



Days of gonadotrophin treatment Analysis 3.5

Estrogen + Antagonist versus Agonist (one study included) - Only one study was included in this subgroup, and this study found that the mean number of days of gonadotrophin therapy was 10.3 (± 1.6) in the study group (n = 14) and 12.8 (± 1.7) in the control group (n = 6), with a P value of 0.002 (Franco Jr 2003).

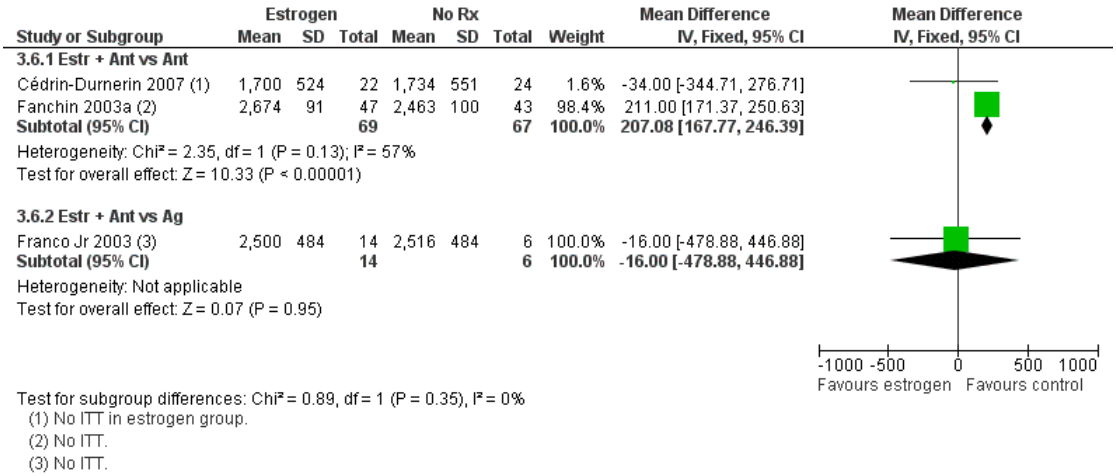
Amount of gonadotrophins administered Analysis 3.6

Estrogen + Antagonist versus Antagonist (two studies included) - Both studies in this subgroup, with a total of 136 women, reported on this outcome and results have been pooled. A statistically significant difference was found with fewer gonadotrophins administered in the group that did not receive pre-treatment with oestrogen (MD 207.08; 95% CI 167.77 to 246.39, P < 0.00001). A moderate amount of heterogeneity was found, with an I^2 statistic of 57%. We could not perform a sensitivity analysis, because there were only two studies that reported the outcome in this subgroup. An overview of characteristics of the studies for this subgroup are reported in Table 3.

Estrogen + Antagonist versus Agonist (one study included) - This study found that the mean amount of gonadotrophins administered was 2,500 IU (± 484) in the study group (n = 14) and 2,516 IU (± 484) in the control group (n = 6), Peto OR -16.0; 95% CI -478.88 to 446.88, P = 0.95 (Franco Jr 2003).

See Figure 19 for the graph and details of this outcome.

Figure 19. Forest plot of comparison: 3 Estrogen versus no Rx, outcome: 3.6 Amount of gonadotrophins administered.



Pregnancy losses Analysis 3.7

Estrogen + Antagonist versus Antagonist (two studies included) - Only one study reported on this outcome and found one pregnancy loss in the study group (n = 25) and five pregnancy losses in the control group (n = 24), Peto OR 0.22; 95% CI 0.04 to 1.17, P = 0.08 (Cédrin-Durnerin 2007).

Estrogen + Antagonist versus Agonist - The only study included in this subgroup found no pregnancy losses in both treatment groups (study group n = 16; control group n = 6).

Ovarian cyst formation Analysis 3.8

Estrogen + Antagonist versus Agonist (one study included) - The only study included in this subgroup found no ovarian cyst formation in both treatment groups (study group n = 16; control group n = 6).

Multiple pregnancies Analysis 3.9

Estrogen + Antagonist versus Antagonist (two studies included) - Only one study reported on this outcome and found no multiple pregnancies in the study group (n = 25) and one in the control group (n = 24), Peto OR 0.13; 95% CI 0.00 to 6.55, P = 0.31 (Cédrin-Durnerin 2007).

Estrogen + Antagonist versus Agonist (one study included) - Only one trial could be included in this subgroup (Franco Jr 2003). The number of multiple pregnancies was two in the study group (n = 14) and none in the control group (n = 6), Peto OR 4.52; 95% CI 0.20 to 101.00, P = 0.34.

OHS syndrome Analysis 3.10

Estrogen + Antagonist versus Agonist (two studies included) - The only study included in this subgroup found no women with OHS syndrome in both treatment groups (study group n = 16; control group n = 6).

Combined OCP versus Progestogen

Only one trial could be included in this intervention (Cédrin-Durnerin 2007). This trial used a GnRH antagonist in both treatment groups. None of the results of this trial were found to be statistically significant.

Live births Analysis 4.1

The number of live births was found to be three in the combined OCP group (n = 21) and five in the progestogen group (n = 23), Peto OR 0.61; 95% CI 0.13 to 2.79, P = 0.53.

Ongoing pregnancies Analysis 4.2

The number of ongoing pregnancies was also found to be three in the combined OCP group (n = 21) and five in the progestogen group (n = 23), Peto OR 0.61; 95% CI 0.13 to 2.79, P = 0.53..

Clinical/ongoing pregnancies Analysis 4.3

The number of clinical pregnancies was five in the combined OCP group (n = 21) and seven in the progestogen group (n = 23), Peto OR 0.72; 95% CI 0.19 to 2.68, P = 0.63.

Oocytes retrieved Analysis 4.4

The mean number of oocytes retrieved was 14 (± 8.3) in the combined OCP group (n = 21) and 12.6 (± 7.3) in the progestogen group (n = 23), Peto OR 1.40; 95% CI -3.24 to 6.04, P = 0.55.

Days of gonadotrophin treatment Analysis 4.5

This outcome was not reported by this study.

Amount of gonadotrophins administered

The mean amount of gonadotrophins administered was 2,174 IU (± 723) in the combined OCP group (n = 21) and 2,010 IU (± 670) in the progestogen group (n = 23), Peto OR 164.00; 95% CI -249.03 to 577.03, P = 0.44.

Pregnancy losses Analysis 4.6

The number of pregnancy losses in both treatment groups was two (study group n = 21; control group n = 23), Peto OR1.10; 95% CI 0.14 to 8.43, P = 0.92.

Ovarian cyst formation

This outcome was not reported by this study.

Multiple pregnancies Analysis 4.7

There were two multiple pregnancies in the combined OCP group (n = 21) and one in the progestogen group (n = 23), Peto OR 2.22; 95% CI 0.22 to 22.56, P = 0.50.

OHS syndrome

This outcome was not reported by this study.

Combined OCP versus Estrogen

Live births Analysis 5.1

COCP + Antagonist versus Estrogen + Antagonist (one study included) - The number of live births was found to be three in the combined OCP group (n = 21) and three in the oestrogen group (n = 25), Peto OR 1.22; 95% CI 0.22 to 6.69, P = 0.82 (Cédrin-Durnerin 2007).

Ongoing pregnancies Analysis 5.2

COCP + Antagonist versus Estrogen + Antagonist (one study included) - The number of ongoing pregnancies was also found to be three in the combined OCP group (n = 21) and three in the oestrogen group (n = 25), Peto OR 1.22; 95% CI 0.22 to 6.69, P = 0.82 (Cédrin-Durnerin 2007).

COCP + Agonist versus Estrogen + Antagonist (one study included) - The number of ongoing pregnancies was one in the combined OCP group (n = 12) and seven in the oestrogen group (n = 13). This is a statistically significant difference Peto OR 0.13; 95% CI 0.03 to 0.70, P =0.02 (Daly 2002).

Clinical/ongoing pregnancies Analysis 5.3

COCP + Antagonist versus Estrogen + Antagonist (one study included) - The number of clinical pregnancies was five in the combined OCP group (n = 21) and four in the oestrogen group (n = 25), Peto OR 1.62; 95% CI 0.38 to 6.90, P = 0.51 (Cédrin-Durnerin 2007).

COCP + Agonist versus Estrogen + Antagonist (one study included) - The number of clinical pregnancies was two in the combined OCP group (n = 12) and eight in the oestrogen group (n = 13). This is a statistically significant difference , Peto OR 0.17; 95% CI 0.03 to 0.80, P =0.02 (Daly 2002).

Oocytes retrieved Analysis 5.4

COCP + Antagonist versus Estrogen + Antagonist (one study included) - The mean number of oocytes retrieved was 14 ± 8.3 in the combined OCP group (n = 21) and 13.1 ± 7 in the oestrogen group (n = 22), Peto OR 0.90; 95% CI -3.70 to 5.50, P = 0.70 (Cédrin-Durnerin 2007).

Days of gonadotrophin treatment

This outcome was not reported by these studies.

Amount of gonadotrophins administered Analysis 5.5

COCP + Antagonist versus Estrogen + Antagonist (one study included) - The mean amount of gonadotrophins administered was 2,174 IU (± 723) in the combined OCP group (n = 21) and 1,700 IU (± 524) in the oestrogen group (n = 22). This is a statistically significant difference, with Peto OR 474.00; 95% CI 95.10 to 852.90, P = 0.01 (Cédrin-Durnerin 2007).

Pregnancy losses Analysis 5.6

COCP + Antagonist versus Estrogen + Antagonist (one study included) - The number of pregnancy losses in the combined OCP group was two (n = 21) and in the oestrogen group the number was one (n = 25), Peto OR 2.43; 95% CI 0.24 to 24.79, P =0.45 (Cédrin-Durnerin 2007).

COCP + Agonist versus Estrogen + Antagonist (one study included) - In each group there was one pregnancy loss (study group n = 12; control group n = 13), Peto OR 1.09; 95% CI 0.06 to 18.49, P = 0.95 (Daly 2002).

Ovarian cyst formation

This outcome was not reported by these studies.

Multiple pregnancies Analysis 5.7

COCP + Antagonist versus Estrogen + Antagonist (one study included) - There were two multiple pregnancies in the combined OCP group (n = 21) and none in the oestrogen group (n = 25), Peto OR 9.40; 95% CI 0.56 to 156.66, P = 0.12 (Cédrin-Durnerin 2007).

OHS syndrome

This outcome was not reported by these studies.

Progestogen versus Estrogen

Only one trial could be included in this subgroup (Cédrin-Durnerin 2007). This trial used a GnRH antagonist in both treatment groups. None of the results of this trial were found to be statistically significant.

Live births Analysis 6.1

The number of live births was found to be five in the progestogen group (n = 23) and three in the oestrogen group (n = 25), Peto OR 1.99; 95% CI 0.44 to 8.94, P = 0.37.

Ongoing pregnancies Analysis 6.2

The number of ongoing pregnancies was also found to be five in the progestogen group (n = 23) and three in the oestrogen group (n = 25), with Peto OR 1.99; 95% CI 0.44 to 8.94, P = 0.37.

Clinical/ongoing pregnancies Analysis 6.3

The number of clinical pregnancies was seven in the progestogen group (n = 23) and four in the oestrogen group (n = 25), with a P value of 0.24.

Oocytes retrieved Analysis 6.4

The mean number of oocytes retrieved was 12.6 (± 7.3) in the progestogen group (n = 23) and 13.1 (± 7) in the oestrogen group (n = 22), with Peto OR 2.23; 95% CI 0.59 to 8.44, P = 0.81.

Days of gonadotrophin treatment

This outcome was not reported by this study.

Amount of gonadotrophins administered Analysis 6.5

The mean amount of gonadotrophins administered was 2,010 IU (± 670) in the progestogen group (n = 23) and 1,700 IU (± 524) in the oestrogen group (n = 22), Peto OR -0.50; 95% CI -4.68 to 3.68, P = 0.08.

Pregnancy losses Analysis 6.6

There were two pregnancy losses in the progestogen group (n = 23) and one in the oestrogen group (n = 25), Peto OR 310.00; 95% CI -40.60 to 660.60, P = 0.51.

Ovarian cyst formation

This outcome was not reported by this study.

Multiple pregnancies Analysis 6.7

There was one multiple pregnancy in the progestogen group (n = 23) and none in the oestrogen group (n = 25), Peto OR 8.06; 95% CI 0.16 to 407.60, P = 0.30.

OHS syndrome

This outcome was not reported by this study.

DISCUSSION

Summary of main results

This systematic review on the role of pre-treatment with the combined OCP, a progestogen or an oestrogen prior to ART cycles, has pooled the results of studies for three of the six interventions. For the other interventions, we have not been able to pool any results, since only one study could be included in the subgroups of these interventions.

No statistically significant results were found for the primary outcome of live births. We were able to pool results of two trials that used progestogen as a pre-treatment and compared this with no pre-treatment or placebo. This showed no evidence for a difference in the number of live births. For the other interventions, we have not been able to pool results of two or more studies, so no sound conclusion can be given.

For the outcome of ongoing pregnancies, we have been able to pool results of two or more studies that compared a pre-treatment with the combined OCP with no pre-treatment. None of these

showed evidence for a treatment effect. We have not been able to pool results for the other interventions.

With regard to the outcome clinical pregnancy rate, we found a statistically significant result in two subgroups of two different interventions. In comparison 1.3.2 (COCP plus antagonist versus antagonist) this difference was in favour of the group not pretreated with the combined OCP, with fewer clinical pregnancies being achieved in the study group. In comparison 1.3.3 (COCP plus antagonist versus agonist), we pooled the results of three studies and found no statistically significant difference. However, in comparison 2.3.1 (progestogen plus agonist versus agonist) there was a statistically significant difference in favour of the group pretreated with the progestogen. In this comparison, the number of clinical pregnancies was increased in the study group. For the other interventions and subgroups, we have not been able to pool results of two or more studies.

For the outcome of the number of oocytes retrieved we have been able to pool results of four subgroups in three different interventions and only one of these showed a statistically significant difference. This difference was found in comparison 3.4.1 (oestrogen plus antagonist versus antagonist), with more oocytes being retrieved after pre-treatment with an oestrogen.

Two other outcomes that showed statistically significant differences were the number of days of gonadotrophin therapy and the amount of gonadotrophins administered. These differences were found in the comparisons 1.5.1 and 1.6.1 (COCP plus antagonist versus antagonist) and comparisons 1.5.2 and 1.6.2 (COCP plus antagonist versus agonist). All these differences were in favour of the groups that did not receive pre-treatment, with fewer days of gonadotrophin therapy and a smaller amount of gonadotrophins administered in the control group. A statistically significant difference with regard to the amount of gonadotrophins administered was also found in the comparison 3.6.1 (oestrogen plus antagonist versus antagonist). This difference was also in favour of the control group. Furthermore we have been able to pool the results of two studies in comparison 2.6.1 (progestogen plus agonist versus agonist), with regard to the number of days of gonadotrophin treatment and we found no evidence for a treatment effect. For the other interventions and subgroups we have not been able to pool any data.

These results are mainly important with regard to the financial aspects of the IVF/ICSI treatment and might be explained because of a longer duration of ovarian suppression. Instead of suppression with only a GnRH analogue as in the control group, the ovaria were also suppressed with a combined OCP or oestrogen in the pre-treatment group. However, this might result in less need for GnRH analogue administration as suggested by Griesinger 2008, but we did not address this outcome in our review.

With regard to the number of pregnancy losses, we have been able to pool the results for three subgroups in two interventions, but we found no evidence for a treatment effect.

The only adverse outcome that showed a statistically significant difference was found in comparison 2.8.1 (progestogen plus agonist versus agonist). The number of ovarian cysts was shown to be increased in the control group that did not receive hormonal pretreatment. This is clinically important, because a frequent reason for cycle cancellation is the occurrence of ovarian cysts. It is unclear whether the formation of ovarian cysts in the studies of this comparison has lead to cycle cancellation, because this was not reported. The lower incidence of ovarian cysts in progestogen pretreated cycles, might explain the higher clinical pregnancy rates because fewer cycles have to be cancelled. This was also suggested in another review on combined OCP pre-treatment (Griesinger 2008).

For the outcome of multiple pregnancies and OHS syndrome we have been able to pool results for one subgroup in the intervention that compared a combined OCP pre-treatment with no pretreatment, but this showed no statistically significant difference. For the other interventions or subgroups we were not able to pool any results with regard to these outcomes.

Overall completeness and applicability of evidence

Although we were able to include 23 studies across 6 comparisons, there were insufficient data to report on the primary outcome of live births. Using subgroups of different GnRH antagonist and agonist protocols also limited the ability to pool data. There were also limited data for many of the secondary outcomes and almost all of the adverse outcomes.

This review did include women with polycystic ovary syndrome (PCOS), but there was only one study of 56 randomised women that only included a diagnosis of PCOS. Five other studies have used PCOS or ovarian cysts as an exclusion criteria. These studies have randomised a total of 1118 women, so almost half of all the women in this review were not diagnosed with PCOS. Because of the small proportion of women with PCOS included in this review, results might not be relevant for these women.

Also, we planned on doing subgroup analysis on poor responders and there were two included randomised trials that used poor response to ovarian stimulation as an inclusion criteria. These studies randomised a total of 203 women. However, we have not been able to pool results of these two studies, since they used a different ovarian stimulation protocol. Therefore, although a relatively large number of poor responder patients is included, this review might not be applicable to women who have a history of poor response.

An outcome that we did not address was the number of days of GnRH analogue treatment. This could be considered in the update as pre-treatment with a combined OCP, progestogen or oestrogen, may result in a reduction in the amount of GnRH analogues administered. This is mainly important with regard to the financial aspect of the treatment.

Quality of the evidence

Because of the few studies in each subgroup (with a maximum of six studies), a solid conclusion regarding the objective of this review is not possible.

In this review we included 23 studies with a total of 2596 women. These 23 studies were distributed to six comparisons and thirteen subgroups. Three of the studies were used in more than one subgroup, due to the existence of three or four study arms.

A possible methodological limitation of the included studies is that an intention-to-treat (ITT) analysis was not carried out on all the outcomes that the studies reported. Most of the studies used an ITT analysis to describe baseline characteristics of the women, but did not analyse the (continuous) data according to a true ITT definition, which describes that all randomised women should be included in the final analyses. Blinding was only used in 13% of the studies but this was not considered a major problem because women in the placebo arm would have been able to recognise which treatment they were receiving because of bleeding patterns. Other smaller concerns were the inconsistency of the outcomes reported. Definitions of oocytes retrieved, cyst formation and clinical pregnancy, differed between studies. Also, different units were used to describe gonadotrophin usage.

Potential biases in the review process

A strength of this review is the grouping of the studies into subgroups regarding the type of down regulation used (agonist or antagonist). Nonetheless, there is still some substantial heterogeneity in a few of the statistically significant outcomes, such as the number of days of gonadotrophin administration, but this may be explained by differences in treatment protocols between studies.

The major limitation of this review is the poor reporting of all outcomes that are important to clinicians prior to making changes to treatment protocols. In particular, the outcomes of live birth rate but also pregnancy losses, cyst formation, cycle cancellation, multiple pregnancies and women with OHS syndrome are missing from the majority of the studies.

Furthermore, we were not able to construct a funnel plot, due to the small number of studies in each subgroup. Therefore we could not examine if publication bias was present.

Agreements and disagreements with other studies or reviews

To our knowledge, there is one systematic review on combined OCP pre-treatment available (Griesinger 2008). This review investigates the effect of a combined OCP pre-treatment in a GnRH antagonist cycle versus no pre-treatment, and included four studies (Cédrin-Durnerin 2007; Huirne 2006b; Kolibianakis 2006; Rombauts 2006). All of these studies are also included in our review, but we have included two more studies in this subgroup (Kim 2005; Obruca 2001). Due to a lack of data, despite contacting the author, or differences in treatment protocols we were not able to pool their results. Because the systematic review of Dr Griesinger included the same studies and investigated almost the same outcomes, it is not surprising that we reach the same conclusions. In his review, Dr Griesinger found no significant effects on ongoing pregnancies. Also, he found a significant difference in favour of the control group with regard to the number of days and amount of gonadotrophin administration.

AUTHORS' CONCLUSIONS

Implications for practice

It is not possible to make recommendations for clinical practice on the basis of this review. Although we did find some significant differences in a few outcomes for three comparisons, more studies are required before major changes should be made to ART protocols. Besides this, there are a few other important aspects to consider when deciding if a pre-treatment with a combined OCP, a progestogen or an oestrogen should be given. First of all, a pre-treatment with one of these drugs results in a longer duration and a higher amount of gonadotrophin treatment, which is expensive. Secondly, the pre-treatment with one of these drugs means the need for a longer duration of the IVF/ICSI cycle and this is a burden to the woman. And last, if pre-treatment with combined OCP, progestogen or oestrogen will be given, this should be clearly explained to the woman, because the need for oral contraceptive drugs might be hard to understand when you are trying to get pregnant.

The positive effect of a pre-treatment with progestogen on the rate of clinical pregnancies found in this review is surprising, since a pre-treatment with a combined OCP seems to yield lower clinical pregnancy rates. In our review we also found that a pre-treatment with progestogen results in the formation of fewer ovarian cysts. This is important, since ovarian cysts have a negative effect on the number of pregnancies, because ART cycles have to be cancelled. However, only one study that used a combined OCP pre-treatment reported on the number of ovarian cyst formation and this study also found a statistically significant difference in favour of the combined OCP group. Unless more research is done on the underlying mechanism that could explain these effects, no implications for practice can be made.

If pre-treatment with progestogens seems to result in a better IVF/ICSI outcome, this could be clinically and financially important. The administration of progestogen is easy, appears to be safe for the woman and it is less expensive than combined OCP pre-treatment.

Implications for research

More and larger RCTs are needed that randomise subfertile women

with regular IVF/ICSI indications, undergoing a pre-treatment with a combined OCP, progestogen or oestrogen in GnRH analogue plus gonadotrophin cycles. Especially pre-treatments with the combined OCP or a progestogen are of interest for further research. The most important outcome that should be addressed is the number of live births. Other outcomes that are important are the formation of ovarian cysts, pregnancy losses and the number of women with OHS syndrome. Furthermore, research on poor responder patients is necessary, because we were unable to include many trials with poor responder patients.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aston 1995

Methods	Parallel group study Number of women randomised: 152 (75 in control group, 77 in study group) Number of withdrawals: 8 (7 in control group: 5 due to endometrioma or cysts and 2 chose not to proceed; 1 in study group due to endometrioma) Number of women analysed:144
Participants	Country: authors are from the United Kingdom Inclusion criteria: women planning to have an IVF cycle on the Southampton IVF programme. Exclusion criteria: an endometrioma or an ovarian cyst seen on vaginal ultrasound scan on day 19 of the menstrual cycle (after recruitment) Mean age and SD Study group: 33.8 ± 4.1 Control group: 33.5 ± 3.5
Interventions	1) Medroxyprogesterone acetate 10 mg/day on cycle days 19-25 + GnRH agonist (buserelin acetate, nasal administration) 200 μg 3 times daily from cycle day 21 + hMG 4 ampoules/day (75 IU FSH and 75 IU LH per ampoule) from day 4 of ensuing menses 2) Placebo on cycle days 19-25 + GnRH agonist (buserelin acetate, nasal administration) 200 μg 3 times daily from cycle day 21 + hMG 4 ampoules/day (75 IU FSH and 75 IU LH per ampoule) from day 4 of ensuing menses Both hMG and GnRH agonist are continued until hCG injection (10,000 IU, IM), administered when the leading 3 follicles reach a diameter of $\geq$ 18 mm and the serum oestradiol level is > 300 pmol/L for every follicle > 14 mm in diameter
Outcomes	Cyst development; intraovarian sonolucent structure with a mean diameter of > 14 mm, measured after 12 days of pituitary suppression Clinical pregnancy rates; not defined
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: 'The hospital pharmacy randomised to contain placebo or progestogen.' Method of randomisation not reported.
Allocation concealment?	Yes	Quote: 'The hospital pharmacy provided a series of consecutively numbered bottles'

Aston 1995 (*Continued*)

Blinding? All outcomes	Yes	Double blind Women in control group received a placebo.
Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawals reported. Withdrawals due to endometrioma slightly imbalanced: 5 in control group, 1 in study group
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	Unclear	Quote: 'No difference was seen between the study group and control group in the indication of IVF and age.' No P values given in table. Only baseline data available of women analysed, but not of all the women randomised

Biljan 1998a

Methods	Academic centre, parallel group study Number of women randomised: 83 women undergoing 102 cycles (51 cycles in control group, 51 cycles in study group; number of women per group not reported) Number of withdrawals: not reported Number of women analysed: only number of cycles analysed reported (n=102)
Participants	Country: authors are from Canada Inclusion criteria: patients who were receiving a long protocol of pituitary suppression in the early follicular phase as a part of IVF-ET treatment. Exclusion criteria: not reported Median age and range: Study group: 35.2 (32.5-39.1) Control group: 33.7 (31.6-38.3)
Interventions	1) Combined OCP on cycle days 1-14 + GnRH agonist (buserelin acetate, long protocol) 500 μg/day start on cycle day 14 + hMG (75 IU FSH and 75 IU LH) or pure FSH (75 IU) start after achievement of pituitary suppression. 2) GnRH agonist (buserelin acetate, long protocol) 500 μg/day start on cycle day 2 + hMG (75 IU FSH and 75 IU LH) or pure FSH (75 IU) start after achievement of pituitary suppression If no pituitary suppression (serum E_2 concentration < 40 pg/mL) is achieved after 14 days of GnRH agonist administration, the dosage of buserelin acetate is increased to 500 μg twice daily + administration of an IM injection of progesterone 100 mg Both hMG/FSH and GnRH agonist are continued until hCG injection, administered when $\geq$ 3 follicles reach a mean diameter of $\geq$ 18 mm

Biljan 1998a (*Continued*)

Outcomes	Clinical pregnancy rate per cycle started; presence of one or more fetal hearts confirmed with US performed at least 4 weeks after embryo transfer Number of patients with a cyst; intraovarian sonolucent structure with a mean diameter of > 14 mm, measured after 7 days of pituitary suppression Number of days of GnRH-a treatment Number of days of gonadotrophin treatment Total quantity of gonadotrophin administered; measured in ampoules Number of follicles and Number of oocytes collected/fertilised Number of embryos replaced Implantation rate
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: 'They were randomised in two groups by drawing sealed envelopes that contained randomly generated numbers.'
Allocation concealment?	Yes	Sealed envelopes
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	No	Numbers and reasons for withdrawals not reported.
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	Only number of cycles per treatment group known, number of women per group not reported. No significant difference in baseline characteristics between groups with regard to age, cause of infertility, number of previous attempts, and E_2, FSH or LH level.

Cédrin-Durnerin 1996

Methods	Cross-over study, no pre-crossover data available. Number of women randomised: 68 (35 cycles in control group, 34 cycles in study group; 1 patient was randomised twice after cancellation for an ovarian cyst). Crossover design: 18 patients in the control group crossed over to the study group, 3 patients in the study group crossed over to the control group. Number of withdrawals: 9 (6 in control group: 1 due to high serum progesterone value on day 6, 4 due to inadequate or poor response to stimulation, 1 due to personal reasons; 3 in study group: 2 due to inadequate or poor response to stimulation, 1 due to ovarian cyst) Number of women analysed after crossover: 52 in study group and 38 in control group
Participants	Country: authors are from France Inclusion criteria: patients < 42 years old who were undergoing an IVF procedure for tubal disease, male factor, endometriosis or unexplained infertility. Exclusion criteria: not reported Mean age and SD both groups: 32.8 ± 0.5
Interventions	1) Norethisterone 10 mg/day for 12-20 days, start on cycle day 15 + GnRH agonist (triptorelin) 100 μg/day, start on post-treatment day 3 + hMG 140-150 IU a.m. start on day 4/5 of GnRH agonist treatment (dose adjustments if necessary). 2) GnRH agonist (triptorelin) 100 μg/day, start on cycle day 1 + hMG 140-150 IU IM start on cycle day 4/5 (dose adjustments if necessary) Both hMG and GnRH agonist are continued until hCG injection (10,000 IU), administered when $\geq$ 2 follicles reach a diameter of $\geq$ 18 mm and serum oestradiol values were ~ 200 pg/mL per follicle > 15 mm
Outcomes	Hormonal values Day of hCG Number of hMG vials Number of oocytes retrieved; defined as mature oocytes or follicles Number of embryos replaced Number of pregnancies; not defined. Number of 'take home babies'
Notes	Power calculation performed: no Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: 'Participating women were randomised...' Method not reported.
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported

Cédrin-Durnerin 1996 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawals reported.
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	Quote: 'There was no difference in the mean age or in the indication of IVF between the groups.' No data on baseline characteristics reported.

Cédrin-Durnerin 2007

Methods	Multicentre (6 IVF centres), parallel group study Number of women randomised: 93 (21 in OCP group, 23 in progestogen group, 25 in oestrogen group, 24 in control group) Number of withdrawals: 3 in oestrogen group (1 did not start any treatment, 1 due to an ovarian cyst and one due to major protocol violation) Number of women analysed: 90 Duration of study: 10 months of recruitment
Participants	Country: authors are from France Inclusion criteria: (i) regular normo-ovulatory cycles (28 to 35 days), (ii) age < 38 years, (iii) BMI between 18 and 30. Exclusion criteria: (i) high levels of baseline serum FSH or E_2 values, (ii) < 5 follicles at the antral follicular count performed on day three of a spontaneous cycle, (iii) a history of high (> 20 oocytes) or low (< 5 oocytes) ovarian response in a previous IVF attempt Mean age and SD: OCP group: 30.8 ± 4.6 Progestogen group: 32.9 ± 2.5 Estrogen group: 31.8 ± 3.2 Control group: 31.2 ± 4.3
Interventions	1) Combined OCP (ethinyl 30 μg + desogestrel 150 μg) daily, start cycle day two or three for 15 to 21 days (stop on a Sunday) + rFSH (recombinant follitropin beta) 150 to 300 IU/day, start post-treatment day five + GnRH antagonist (ganirelix acetate) 0.25 mg/day, start when leading follicle reaches 14 mm in diameter. 2) Norethisterone 10 mg/day, start cycle day 15 for 10 to 15 days (stop on a Sunday) + rFSH (recombinant follitropin beta) 150-300 IU/day, start post-treatment day five + GnRH antagonist (ganirelix acetate) 0.25 mg/day, start when leading follicle reaches 14 mm in diameter. 3) Micronized 17-βE_2 2 mg twice daily, 10 to 15 days, start 10 days before the presumed menses (stop on a Sunday) + rFSH (recombinant follitropin beta) 150 to 300 IU/day, start post-treatment day five + GnRH antagonist (ganirelix acetate) 0.25 mg/day, start when leading follicle reaches 14 mm in diameter. 4) rFSH (recombinant follitropin beta) 150 to 300 IU/day, start day three after spontaneous menses + GnRH antagonist (ganirelix acetate) 0.25 mg/day, start when leading follicle reaches 14 mm in diameter

	rFSH dose according to age, BMI and previous responses to stimulation; after five days of treatment dose adjustment according to ovarian response Both rFSH and GnRH antagonist are continued until hCG injection (10,000 IU), administered when ≥ three mature (≥ 17 mm) follicles were obtained
Outcomes	Number of live births Number of positive pregnancy tests Clinical pregnancy rate; not defined Ongoing pregnancy rate; a pregnancy developing beyond 12 weeks Multiple pregnancy rate; not defined Hormonal profiles during the 5-day wash-out period Follicular growth Antagonist duration Pre-treatment duration Number of retrievals FSH dose Transferred embryos
Notes	Power calculation performed: no Intention-to-treat analysis performed: no (not for oestrogen group)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: 'Random allocation sequence was generated from a table of random numbers. .. Randomization was stratified by centre.. .'
Allocation concealment?	Yes	Quote: 'Random allocation sequence was concealed to each physician who enrolled and randomized patients.' Sealed envelopes
Blinding? All outcomes	No	Quote: 'This study was not blind.'
Incomplete outcome data addressed? All outcomes	No	The reason for one withdrawal in the oestrogen group is unclear (quote: 'did not start any treatment')
Free of selective reporting?	Unclear	Hormonal values planned and (incompletely) reported in abstract and also (completely) reported in journal article. Other planned outcomes not reported.

Cédrin-Durnerin 2007 (*Continued*)

Free of other bias?	No	No significant baseline imbalance with regard to age and BMI. No other characteristics mentioned

Daly 2002

Methods	Cross-over study Number of women randomised: 25 (13 study group, 12 in control group) Number of withdrawals: not reported Number of women analysed: unclear
Participants	Country: authors are from United States of Amerika Inclusion criteria: women, < 41 years of age, who were anticipated to have limited ovarian reserve (LOR) based on transvaginal ultrasound showing limited follicles on cycle day 2-3 or hormonal values (inhibin B, FSH, E2) Exclusion criteria: not reported Mean age and SD: not reported Poor response: yes ('limited ovarian reserve')
Interventions	1) Estradiol 2 mg in the luteal phase of the preparation cycle + FSH 300 IU, start cycle day 2 + GnRH antagonist (ganirelix acetate) start in late follicular phase + hMG (375 IU FSH + 150 IU LH), timing not reported. 2) Combined OCP + GnRH agonist (leuprolide acetate, microdose) + hMG (300 IU FSH + 75 IU LH). Timing of administration of combined OCP, hMG and GnRH agonist not reported
Outcomes	Ongoing pregnancy; a viable pregnancy, method of assessment is not reported Clinical pregnancy; not defined Number of mature oocytes Number of good embryos Implantation rate Cancellation rate
Notes	Power calculation performed: unclear Intention-to-treat analysis performed: unclear

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	'Randomized', method not reported.
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	No	Unblinded

Daly 2002 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Only abstract available. Numbers and reasons for withdrawals not reported
Free of selective reporting?	Unclear	Data on all planned outcomes reported. Pre-crossover data on primary outcome reported, but on some secondary outcomes (implantation rate, mature oocytes, good embryos) only post-cross-over data is reported
Free of other bias?	No	No data on baseline characteristics reported.

Ditkoff 1996

Methods	Parallel group study Number of women randomised: 105 (58 in control group and 47 in study group) Number of withdrawals: 0 Number of women analysed: 105 Length of follow up: until end of treatment cycle.
Participants	Country: United States of America Inclusion criteria: day 3 FSH values < 15 mIU/mL Exclusion criteria: not reported Mean age and SD: Study group: 36.7 ± 4.8 Control group: 35.8 ± 4.57
Interventions	1) Norethindrone acetate (NETA, oral) 10 mg/day on cycle days one to eight + GnRH agonist (leuprolide acetate, s.c.) 1 mg/day, start cycle day one + hMG 225 IU/day (IM administration), start when serum oestradiol level was < 30 pg/ml. 2) GnRH agonist (leuprolide acetate, s.c.) 1 mg/day, start cycle day 1 + hMG 225 IU/day (IM), start when serum oestradiol level was < 30 pg/mL Both hMG and GnRH agonist are continued until hCG injection (10,000 IU, IM), administered when the leading follicles reaches a diameter of ≥ 18 mm
Outcomes	Number of deliveries/ongoing pregnancies; positive heart activity on US. Number of clinical pregnancies; evidence of a clinical gestational sac. Days until suppression Number of cysts cycles; intraovarian sonolucent structure with a mean diameter of > 14 mm, measured after 8 days of pituitary suppression Number of oocytes retrieved Days of ovarian stimulation Number of ampoules of hMG
Notes	Power calculation performed: no Intention-to-treat analysis performed: no

Ditkoff 1996 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: 'Patients were randomly assigned by tossing a coin to one of two groups.'
Allocation concealment?	Yes	Centralised randomisation process.
Blinding? All outcomes	No	No blinding
Incomplete outcome data addressed? All outcomes	Yes	No withdrawals
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	No table of baseline characteristics. Quote: 'The various infertility diagnoses were distributed equally between the control and study groups.'

Engmann 1999

Methods	Parallel group study Number of women recruited: 123 Number of women excluded: six (two due to ovarian cysts ≥ 15 mm, two due to raised early follicular phase serum FSH, two did not undergo IVF) Number of women randomised: 117 (54 in control group, 63 in study group) Number of withdrawals: one (in study group, due to violation of the study protocol) Number of women analysed: 116 Duration of study: one year of recruitment Source of funding: Schering Health Care Limited, West Sussex, United Kingdom, supplied the norethindrone
Participants	Country: authors are from the United Kingdom and Canada Inclusion criteria: (i) age 18 to 44 years at time of screening, (ii) duration of infertility ≥ one year, (iii) early follicular phase serum FSH ≤ 11.0 IU/L, (iv) good physical and mental health, (v) suitability for the long-term buserelin protocol for desensitization. Exclusion criteria: (i) endometrioma of the ovary, (ii) ovarian cysts (≥ 15 mm) in the early follicular phase, (iii) known contraindications to the use of progestogen, GnRH agonists or hMG Mean age and SD: Study group: 35.3 ± 4.3 Control group: 33.8 ± 5.5

Engmann 1999 (*Continued*)

Interventions	1) Norethindrone 10 mg on cycle day 1 and 5 mg twice daily on cycle day two to five + GnRH agonist (buserelin acetate, s.c., long protocol) 500 μg/day, start on cycle day 2 (dose adjustment after pituitary suppression to 200 μg/day) + hMG (Normegon, 75 IU FSH) two to five ampoules daily or rFSH, start when serum $E_2 \leq 150$ pmol/L. 2) GnRH agonist (buserelin acetate, s.c., long protocol) 500 μg/day start on cycle day two (dose adjustment after pituitary suppression to 200 μg/day) + hMG (Normegon, 75 IU FSH) two to five ampoules daily or rFSH, start when serum $E_2 \leq 150$ pmol/L. Pituitary suppression is achieved when there is an absence of follicular activity and endometrial thickness < 5 mm hMG or rFSH dose according to patient's age, previous response, basal serum FSH levels and PCO Both hMG/rFSH and GnRH agonist are continued until hCG injection (10,000 IU, IM), administered when two or three leading follicles are $\geq$ 18 mm in diameter
Outcomes	Incidence of functional ovarian cysts ($\geq$ 10 mm, measured after one week of GnRH agonist) Number of days required to achieve pituitary desensitization Number of hospital visits before ovarian stimulation Number of preovulatory follicles and mature oocytes Fertilization rate Number of good-quality embryos produced and transferred Implantation rate Clinical pregnancy rate; a positive pregnancy test with evidence of a gestational sac Amount of gonadotrophins administered; measured in ampoules Pregnancy loss
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: 'Eligible patients were randomly assigned in a ratio of 1:1 by means of computer-generated random numbers. To ensure similar distributions of age in the two groups, separate randomization schedules were drawn up for women < 40 years old and women $\geq$ 40 years old by use of stratified randomized blocks.'
Allocation concealment?	Yes	Quote: 'Selection into the groups (and of administration of the appropriate treatment protocol) was performed by the clinic nurses by using a series of consecutively numbered sealed envelopes (one for each age group).'

Engmann 1999 (*Continued*)

Blinding? All outcomes	Yes	Quote: 'Although the patient could guess her treatment status, treatment allocation was not recorded in the clinical notes, and all clinicians were blinded to the status of study participants until the trial was over.'
Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawals reported.
Free of selective reporting?	Yes	Data on all planned outcomes reported.
Free of other bias?	Yes	No significant baseline imbalance between groups with regard to age, duration of infertility, previous attempts, baseline serum FSH, polycystic ovaries and cause of infertility

Fanchin 2001

Methods	Cross-over study, no pre-cross-over data available. Crossover design: 'Women randomly started the protocol by control or E2 pre-treated cycles.' Thereafter, all women did a second (cross-over) cycle. Number of women randomised: 14 (all these women underwent two cycles of treatment; one E2 pre-treated cycle and one control cycle) Number of withdrawals: not reported Number of women analysed: not reported
Participants	Country: authors are from France Inclusion criteria: not reported Exclusion criteria: not reported Mean age and SD: not reported
Interventions	1) 17β-E2 (oral) 4 mg/day, start cycle day 20, stop day 2 next cycle + follicular assessment on day three. 2) Follicular assessment on day three in two successive menstrual cycles
Outcomes	Value of FSH, E_2 and Inhibit B Ovarian volume Number of follicles Size of follicles
Notes	Power calculation performed: unclear Intention-to-treat analysis performed: unclear

Risk of bias

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

Fanchin 2001 (*Continued*)

Adequate sequence generation?	Unclear	Quote: 'Women randomly started...' Method not reported.
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Unclear	Numbers and reasons for withdrawals not reported.
Free of selective reporting?	No	Data on planned outcomes 'follicular development' and 'follicular size on day 3' reported. No other planned outcomes reported, especially no data on pregnancy rates. (Abstract)
Free of other bias?	No	Number of women per group not reported. Baseline characteristics not reported.

Fanchin 2003a

Methods	Parallel group study Number of women randomised: 100 (number of women per group not reported) Number of withdrawals: 10 (four due to personal reasons and six due to major protocol violation) Number of women analysed: 90 (47 in study group and 43 in control group) Duration of study: one IVF-ET cycle, from day 20 of the previous cycle until day of hCG administration (information obtained from contact person)
Participants	Country: authors are from France Inclusion criteria: (i) age $\leq$ 38 years, (ii) regular, ovulatory menstrual cycles every 25 to 35 days, (iii) both ovaries present, (iv) no current or past diseases affecting ovaries or gonadotrophin or sex steroid secretion, clearance or excretion, (v) BMI ranging from 18 to 27 kg/m^2, (vi) no hormone therapy during the past 6 weeks, (vii) adequate visualization of both ovaries in transvaginal ultrasound scans. Exclusion criteria: not reported Median age and range Study group: 33 (26-38) Control group: 33 (25-38)
Interventions	1) Micronized 17β-E_2 (oral tablets) 4 mg/day, start cycle day 20 until day two of the next cycle + rFSH 225 IU/day (s.c.) on cycle days three to seven + GnRH antagonist (cetrorelix acetate, s.c.) three mg single dose when $\geq$one follicle > 13 mm in diameter. 2) rFSH 225 IU/day (s.c.) on cycle days three to seven + GnRH antagonist (cetrorelix acetate, s.c.) three mg single dose when $\geq$ one follicle > 13 mm in diameter rFSH dose adjustments according to follicle growth determined by serum E_2 levels and

Fanchin 2003a (*Continued*)

	ultrasound monitoring.
Outcomes	Days of GnRH antagonist administration Day of hCG administration Dose of gonadotrophins Number of mature follicles Number of embryos transferred Clinical pregnancy rates per cycle; presence of a gestational sac with fetal heart activity at 6 weeks on US scan
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: 'Women randomly received...', '...according to a computer-generated, blocked randomization list'
Allocation concealment?	Yes	Quote: 'Treatment allocation was decided by an independent person.'
Blinding? All outcomes	No	No blinding, information obtained from contact person
Incomplete outcome data addressed? All outcomes	No	Only total number of withdrawals reported, not how many per group
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	Number of women randomised per group not reported, only number of women analysed per group. No difference in baseline characteristics with regard to age, indication for IVF-ET, duration of infertility, rank of the current IVF-ET attempt, menstrual cycle length, day 3 serum FSH and E_2.

Franco Jr 2003

Methods	Parallel group study Number of women recruited: 22 Number of women randomised: 22 (16 in study group, six in control group) Number of withdrawals: two (in study group, due to spontaneous pregnancies) Number of women analysed: 20
Participants	Country: authors are from Brazil Inclusion criteria: patients without specific ovulatory dysfunction, aged ≤ 37 years, that would be submitted to ovarian stimulation Exclusion criteria: not reported Mean age and SD: Study group: 32.2 ± 2.1 Control group: 31.8 ± 1.9
Interventions	1) Estradiol valerate 4 mg/day for 14 days, start cycle day 21 + rFSH 150-300 IU (fixed dose for 5 days), start post-treatment day 1 + GnRH antagonist (ganirelix acetate) 0.25 mg/day, start when follicular diameter ≥ 15 mm. 2) GnRH agonist (nafarelin acetate, nasal) 200 μg twice daily, start cycle day 21 + rFSH 150-300 IU (fixed dose for 5 days), start stimulation day 14 Both rFSH and GnRH analogues are continued until hCG injection (5,000-10,000 IU) , administered when ≥ 2 follicles are ≥ 17 mm in diameter
Outcomes	Clinical pregnancy rate; one or more fetal hearts confirmed with US, performed at least 4 weeks after embryo transfer Ovarian cyst; intraovarian sonolucent structure with a mean diameter of > 14 mm, time of measurement not reported OHS syndrome; not defined Values of LH, estradiol, progesterone Dose of FSH Number of collected oocytes Number of oocytes in metaphase II Fertilisation rate Number of transferred embryos Embryo implantation rate Gestation rate per embryo transfer
Notes	Power calculation performed: no Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was done by drawing lots after constructing a table of distribution. 2:1 randomisation (study:control)

Franco Jr 2003 (*Continued*)

Allocation concealment?	No	After drawing lots, the clinicians and the participants could see in the table to which treatment they were assigned to
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	No withdrawals
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	No significant difference in baseline characteristics with regard to age. No other baseline characteristics reported

Hugues 1994

Methods	Parallel group study Number of women randomised: 45 (25 in control group, 20 in study group) Number of withdrawals: not reported Number of women analysed: not reported
Participants	Country: authors are from France Inclusion criteria: not reported Exclusion criteria: not reported Mean age and SD: not reported
Interventions	1) Norethisterone 10 mg/day for 10-15 days + GnRH agonist (DTRP6-LHRH) 100 μg/day. 2) GnRH agonist (DTRP6-LHRH) 100 μg/day. Timing of treatments not reported.
Outcomes	Values of estradiol and progestogen
Notes	Power calculation performed: unclear Intention-to-treat analysis performed: unclear

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	'Randomised', method not reported.
Allocation concealment?	Unclear	Not reported

Hugues 1994 (*Continued*)

Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Unclear	Numbers and reasons of withdrawals not reported.
Free of selective reporting?	No	Planned outcomes not reported. No data on pregnancy rates.
Free of other bias?	No	Baseline characteristics not reported.

Huirne 2006a

Methods	Multicentre (8 IVF centres), parallel group study Number of women recruited: 216 Number of women excluded: 34 (reasons not reported) Number of women randomised: 182 (91 in study group, 91 in control group) Number of withdrawals: 22 (10 in study group: one due to hepatitis B, one due to non-compliance, one due to personal reasons, two due to insufficient follicular response, one due to conversion to IUI, one due to absence of mature oocytes, three due to absence of viable embryos; 12 in control group:two due to spontaneous pregnancy, three due to failure of desensitization, one due to personal reasons, one due to stimulation failure, three due to absence of 'mature' oocytes, two due to failure of fertilisation) Number of women analysed: 182
Participants	Country: authors are from The Netherlands, Belgium, France and Austria Inclusion criteria: (i) regular IVF/ICSI indication, (ii) a male partner with viable sperm in the ejaculate, (iii) aged between 18 to 39 years. Exclusion criteria: (i) any previous ART cycles with < three oocytes or ≥ three consecutive ART cycles without a clinical pregnancy, (ii) any contraindication to ART, gonadotrophins or OCPs, (iii) a significant systemic disease Mean age and SD: Study group: 32.8 ± 3.8 Control group: 32.2 ± 4.2
Interventions	1) Combined OCP (ethinyl E_2 30 μg + levonorgestrel 150 μg) daily, start within 5 days of onset of menses for 21-28 days (stop on a Sunday) + r-hFSH 150-225 IU/day, start post-treatment day 5 (= stimulation day 1) + GnRH antagonist (cetrorelix acetate, s.c.) 0.25 mg/day, start stimulation day six. 2) GnRH agonist (buserelin acetate, s.c.) 500 μg/day, start cycle day 18-22 (reducing dose to 200 μg/day when down-regulation is achieved) + r-hFSH 150 to 225 IU/day, start when down-regulation is achieved After five days of r-hFSH-treatment, the dose can be adjusted by steps of 75 IU (maximal dose 450 IU/day), according to the ovarian response Both r-hFSH and GnRH analogues were continued until hCG injection, administered when the largest follicle reaches a mean diameter of ≥ 18 mm and ≥ 2 other follicles had a mean diameter of ≥ 16 mm

Outcomes	Ongoing pregnancy rate; positive heart activity at a gestational age of 12 weeks Clinical pregnancy rate; presence of one or more fetal sacs with or without heart activity confirmed with US, performed at least 4 weeks after embryo transfer Numbers of oocytes retrieved per patient Multiple clinical pregnancies Total number of oocyte retrievals performed on weekends or public holidays Cancellation rate Drug requirements Total number of (good quality) embryos Implantation rate
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: '182 were randomly allocated to...', 'The treatment assigned to each patient was determined according to a computer-generated concealed randomization list. Randomization was performed by centre.'
Allocation concealment?	Unclear	'Concealed randomization list', method not reported.
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawals reported.
Free of selective reporting?	Unclear	Data on all planned outcomes reported.
Free of other bias?	Yes	No significant difference in baseline characteristics with regard to age, race, duration of infertility, cause of infertility, smoking habits, primary infertility, number of previous ART attempts, number of follicles, endometrial thickness, FSH levels and estradiol levels. P value of BMI is 0.04.

Huirne 2006b

Methods	Academic, Multicentre, parallel group study Number of women randomised: 64 (32 in study group, 32 in control group) Number of withdrawals: one (in study group, due to unwillingness to take OCP) Number of women analysed: 63 Source of funding: Serono Geneva supplied the antide.
Participants	Country: The Netherlands and Belgium Inclusion criteria: (i) a regular IVF or ICSI indication (i.e. idiopathic infertility after six unsuccessful IUIs, infertility based on a male or tubal factor), (ii) a spontaneous, regular ovulatory menstrual cycle, (iii) two ovaries and a normal uterine cavity, (iv) age 18 to 38 years Exclusion criteria: (i) FSH $\geq$ 12 IU/L on cycle day two to four (ii) BMI > 30 kg/m^2, (iii) abnormal gynaecological bleeding, (iv) an extrauterine pregnancy within the last three months, (v) previous ART cycles with < three oocytes or severe OHS syndrome, (vi) any contraindication to receive gonadotrophins or OCP, (vii) PCOS Mean age and SD: Study group: 32.3 ± 4.0 Control group: 33.3 ± 3.8
Interventions	1) Combined OCP (ethinyl estradiol 30 μg + levonorgestrel 150 μg) for 14-28 days, start cycle day 2 or 3 + rFSH 150-300 IU, start post-treatment day 2 or 3 (= stimulation day 1) + GnRH antagonist (antide) 0.5 mg/mL daily, start stimulation day 6. 2) rFSH 150-300 IU, start on cycle days 2 or 3 (= stimulation day 1) + GnRH antagonist (antide) 0.5 mg/mL daily, start on stimulation day 6 rFSH dose adjustments after 5 days of stimulation (up to a maximum of 450 IU), according to number and size of oocytes and risk for OHS syndrome Both rFSH and GnRH antagonist are continued until hCG injection (6,500 IU), administered when $\geq$ 1 follicle reached a diameter of $\geq$ 18 mm + $\geq$ 2 follicles reached a diameter of $\geq$ 16 mm
Outcomes	Ongoing pregnancy rate; positive heart activity at a gestational age of 12 weeks Clinical pregnancy rate; presence of $\geq$ one intrauterine sac confirmed with US at a gestational age of six weeks. Number of oocytes retrieved Ovarian cysts; not defined Number and size of follicles Cumulative dose of rFSH Duration of r-FSH treatment Implantation rates Serum hormone concentrations Endometrial thickness Bleeding pattern
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description

Huirne 2006b (*Continued*)

Adequate sequence generation?	Yes	Quote: '64 patients were randomly allocated according to a computer-generated, blocked randomization list. The randomisation was stratified by centre.'
Allocation concealment?	Yes	Quote: 'Treatment allocation was decided by an independent person from an independent monitoring company...'
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed? All outcomes	Yes	Reason for withdrawal reported.
Free of selective reporting?	Yes	Data on all planned outcomes reported.
Free of other bias?	Yes	No significant differences in baseline characteristics with regard to age, BMI, cycle length, primary infertility, smoking habits, duration of infertility, type of infertility and antral follicle count

Hwang 2004

Methods	Single centre, parallel group study Number of women recruited: 60 Number of women excluded: 4 (2 refused to participate, 2 did not meet inclusion criteria) Number of women randomised: 56 (27 in study group, 29 in control group) Number of withdrawals: 7 (2 in study group: 1 due to poor ovarian response, 1 due to personal reasons; 5 in control group: 2 due to inadequate ovarian response, 3 due to risk of severe OHS syndrome) Number of women analysed: 49
Participants	Country: Taiwan Inclusion criteria: polycystic ovary syndrome. Exclusion criteria: (i) diagnosis of congenital adrenal hyperplasia, Cushing's syndrome, androgen-producing tumours, hyperprolactinaemia or thyroid dysfunction, (ii) age > 38 years, (iii) serum FSH levels > 12 mIU/mL Mean age and SD: Study group: 31.4 ± 3.5 Control group: 31.7 ± 3.7
Interventions	1) Combined OCP (Diane-35, oral) on cycle days five to 25 for 3 consecutive cycles + GnRH antagonist (cetrorelix acetate, s.c.) 0.25 mg single dose on post-treatment day 3, 0.125 mg/day on post-treatment days four to nine, and 0.25 mg/day start post-treatment day 10 + hMG 150 IU/day, start post-treatment day four. 2) GnRH agonist (buserelin acetate, long protocol) 500 μg/day start day three of induced

	or spontaneous menstruation, and 250 μg/day start day of ensuing pituitary down regulation + hMG 150 IU/day for six days start when pituitary down regulation is achieved hMG dose can be adjusted according to patient's follicular response Pituitary down regulation is achieved when serum E_2 levels are < 50 pg/mL and there is an absence of ovarian cysts > 10 mm in diameter Both GnRH analogues and hMG are continued until hCG injection (10,000 IU, IM), administered when $\geq$2 follicles reached 18 mm in diameter with adequate E_2 response.
Outcomes	Fertilisation Clinical pregnancy; presence of one or more fetal hearts confirmed with US, performed 7 weeks after embryo transfer Implantation rates Serum LH and testosterone status upon starting and during hMG administration Total days and amount of gonadotrophins administered; measured in ampoules Pregnancy loss Multiple pregnancy rate; ongoing or live born OHS syndrome; not defined
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: 'Randomization was done by opening sealed envelopes containing computer-generated block randomization numbers with a block size of 10.'
Allocation concealment?	Yes	Sealed envelopes
Blinding? All outcomes	Yes	Quote: 'The laboratory staff were blinded to the stimulation protocol.' Unclear if treating physicians were blinded
Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawals reported. Slight imbalance in numbers of withdrawal due to risk of severe OHS syndrome: 0 in study group and three in control group
Free of selective reporting?	Yes	Data on all planned outcomes is reported.
Free of other bias?	Unclear	No significant difference in baseline characteristics with regard to age, duration of infertility, BMI and hormonal levels

Kim 2005

Methods	Parallel group study Number of women randomised: 82 (27 in 'combined OCP + GnRH antagonist' group; 27 in GnRH antagonist group; and 28 in GnRH agonist group). Number of withdrawals: 0 Number of women analysed: 82 Duration of study: follow up until 12th week of pregnancy (information obtained from author)
Participants	Country: authors are from South Korea Inclusion criteria: patients who were defined as low responders (defined as patients with repeated high basal serum levels of FSH > 8.5 IU/L and/or total basal antral follicle count of ≤ five), aged 28 to 42 years Exclusion criteria: not reported Mean age and SD: combined OCP + GnRH antagonist group: 35.0 ± 3.4 GnRH antagonist group: 34.8 ± 3.2 GnRH agonist group: 35.8 ± 3.1 Poor response: Yes
Interventions	1) Combined OCP + GnRH antagonist + rFSH 2) GnRH antagonist + rFSH 3) GnRH agonist (low dose, long protocol) + rFSH
Outcomes	Live births Clinical pregnancy rate; presence of an intrauterine gestational sac confirmed with US performed four weeks after oocyte retrieval Ongoing pregnancy rate; evidence of a gestational sac with fetal heart motion at 12 weeks of later confirmed with US Total dose and duration of rhFSH Number of mature oocytes Fertilisation rate Number of grade I, II embryos Miscarriage rate Multiple pregnancy rate
Notes	Power calculation performed: yes Intention-to-treat analysis performed: yes

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	'Randomized', computerised allocation (information obtained from author)
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	No	This trial was not blinded

Kim 2005 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Number and reasons of withdrawals not reported.
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	Quote: 'Patient characteristics were comparable among three groups.' No data on baseline characteristics available.

Kolibianakis 2006

Methods	Acadamic, single centre, parallel group study Number of women randomised: 504 (250 in study group, 254 in control group) Number of withdrawals: 79 (36 in study group: 28 due to personal reasons, six due to abnormal steroid levels, two due to spontaneous pregnancy; 43 in control group: 31 due to personal reasons, 10 due to abnormal steroid levels, two due to spontaneous pregnancy) Number of women analysed: 425 Duration of study: three years of recruitment Source of funding: the Fund for Scientific Research Flanders
Participants	Country: Belgium Inclusion criteria: (i) age < 39 years, (ii) $\leq$ three previous ART attempts, (iii) BMI 18-29 kg/m^2, (iv) levels of FSH < 10 IU/L, (v) levels of LH < 10 IU/L Exclusion criteria: (i) polycystic ovaries, (ii) endometriosis > stage II, (iii) poor response to ovarian stimulation Mean age and SD: Study group: 31.2 ± 0.3 Control group: 31.5 ± 0.3
Interventions	1) Combined OCP (ethinyl estradiol 30 μg + desogestrel 150 μg) for 14 days, start cycle day one + rFSH 200 IU/day (fixed dose), start post-treatment day 5 + GnRH antagonist (ganirelix acetate) 2) rFSH 200 IU/day (fixed dose), start cycle day 2 + GnRH antagonist (ganirelix acetate) Timing of GnRH antagonist not reported. Both rFSH and GnRH antagonist are continued until hCG injection (10,000 IU), administered when $\geq$ 3 follicles $\geq$ 17 mm in diameter
Outcomes	Ongoing pregnancies per started cycle; developing beyond 12 weeks Stimulation length Gonadotrophin consumption Early pregnancy loss; the proportion of patients with initially positive hCG in whom pregnancy failed to develop before 12 weeks of gestation
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Kolibianakis 2006 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: 'Randomized on the basis of a computer-generated list'
Allocation concealment?	No	Quote: '... randomised at the outpatient clinic by the treating physician.', 'The sequence of allocation was not concealed and thus it was possible for the treating physician to be aware of the next treatment to be allocated.'
Blinding? All outcomes	No	Not reported, but treating physician is not blinded as this was the person to allocate the participants
Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawals reported.
Free of selective reporting?	Yes	Data on all planned outcomes reported.
Free of other bias?	Yes	No significant differences in baseline characteristics with regard to age, BMI, primary/secondary infertility, duration of infertility, number of previous IVF trials, indication for treatment

Obruca 2001

Methods	Parallel group study Number of women randomised: 150 (75 in study group, 75 in control group) Number of withdrawals: not reported Number of women analysed: unclear
Participants	Country: authors are from Austria Inclusion criteria: patients undergoing COS and IVF Exclusion criteria: not reported Mean age and SD: not reported
Interventions	1) Combined OCP (ethinyl oestradiol 30 μg + desogestrel 150 μg) daily, start cycle day one for 18 to 28 days (stop on a Sunday) + rFSH 150 IU/day, start post-treatment day five (= stimulation day one) + GnRH antagonist (cetrorelix acetate) 0.25 mg/day, start stimulation day six. 2) rFSH 150 IU/day, start cycle day three (= stimulation day 1) + GnRH antagonist (cetrorelix acetate) 0.25 mg/day, start stimulation day six Both rFSH and GnRH antagonist are continued until final follicular maturation

Obruca 2001 (*Continued*)

Outcomes	Number of cancelled cycles Number of oocytes Number of transferred embryos Clinical pregnancy rate; not defined Number of weekend oocyte retrievals
Notes	Power calculation performed: unclear Intention-to-treat analysis performed: unclear

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	'Randomized', method not reported.
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Unclear	Number and reasons for withdrawals not reported.
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	No data on baseline characteristics reported.

Raoofi 2008

Methods	Academic, single centre, parallel group study. Number of women randomised: 54 women (number of women per group not reported) Number of withdrawals: three women were excluded due to incomplete data Number of women analysed: 51 Duration of study: one year of recruitment Source of funding: Yazd IVF centre, Yazd, Iran
Participants	Country: Iran Inclusion criteria: patients who were undergoing IVF and ICSI Exclusion criteria: not reported Mean age and SD: Study group: 31.48 ± 5.82 Control group: 35.27 ± 4.13
Interventions	1) Combined OCP (ethinyl estradiol 30 μg + desogestrel 150 μg), on cycle days one to 14 + GnRH agonist (triptorelin acetate depot i.m.) 3.75 mg single dose on post-treatment day one + hMG (75 IU FSH + 75 IU LH), start post-treatment day 2

	2) GnRH agonist (triptorelin acetate depot IM) 3.75 mg single dose on cycle day one + hMG (75 IU FSH + 75 IU LH), start cycle day one
Outcomes	Cyst formation > 28 mm; measured seven and 14 days after pituitary suppression Number of follicles Number of oocytes retrieved Implantation rate Clinical pregnancy rate; presence of one or more fetal hearts confirmed with US performed at least 4 weeks after embryo transfer
Notes	Power calculation performed: no Intention-to-treat analysis performed: unclear

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	'Randomized allocation method', method not reported.
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	No	Quote: 'Three patients were excluded from the study because of incomplete data.'
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	No	Number of women per group not reported. Quote: 'The etiology and duration of infertility were equally distributed among the groups.' No table of characteristics available

Rombauts 2006

Methods	Multicentre (ten IVF centres), parallel group study Number of women randomised: 351 (117 per treatment group) Number of withdrawals: 19 (five due to spontaneous pregnancy: two in OCP group and three in GnRH-antagonist group). Other reasons not reported. Number of women analysed: 332 (111 in OCP group, 110 in GnRH-antagonist group and 111 in GnRH-agonist group)
Participants	Country: Australia, Denmark, Jordan and Norway. Inclusion criteria: (i) healthy females of infertile couples, (ii) age 18-39 years, (iii) BMI between 18-29 kg/m^2, (iv) body weight $\leq$ 90 kg, (v) a normal menstrual cycle with a

	range of 24-35 days and an intra-individual variation of ± 3 days Exclusion criteria: (i) contraindications for the use of gonadotrophins, (ii) endocrine abnormalities (e.g. PCOS), (iii) > 3 unsuccessful controlled ovarian stimulation cycles, (iv) history of low or no ovarian response during FSH/hMG treatment, (v) clinically relevant abnormal laboratory values (including hormones) or medical examination findings Mean age and SD: OCP group: 32.7 ± 3.9 GnRH-antagonist group: 32.1 ± 3.7 GnRH-agonist group: 32.2 ± 4.0
Interventions	1) Combined OCP (ethinyl oestradiol 30 μg + desogestrel 150 μg) daily, start cycle day one for 14-28 days (depending on the planned start of rFSH treatment) + rFSH (follitropin beta, s.c.) 200 IU/day, start post-treatment day two (= stimulation day 1) + GnRH antagonist (ganirelix acetate, s.c.) 0.25 mg/day, start stimulation day 5 or 6. 2) rFSH (follitropin beta, s.c.) 200 IU/day, start cycle day two or three (= stimulation day one) + GnRH antagonist (ganirelix acetate, s.c.) 0.25 mg/day, start stimulation day five or six. 3) GnRH agonist (nafarelin acetate, intranasal) 0.8 mg/day, start cycle day 21 to 24 + rFSH (follitropin beta, s.c.) 200 IU/day, start when down regulation (i.e. serum estradiol ≤ 50 pg/ml) is achieved (after 2-4 weeks of GnRH agonist treatment) After five to six days of rFSH treatment, the dose could be adjusted depending on the ovarian response as assessed by ultrasound rFSH and GnRH analogues are both continued until hCG injection (10,000 IU, s.c. or IM), administered when ≥ three follicles ≥ 17 mm in diameter, or ≥ one follicle ≥ 20 mm in diameter
Outcomes	Ongoing pregnancy rate; assessed by US at ≥ 12 to 16 weeks Number of cumulus-oocyte complexes Number of grade one or two embryos Number and size of follicles Serum hormone values Duration of rFSH treatment Total rFSH dose Number of good quality embryos Implantation rate Incidences of LH rises Pregnancy loss OHS syndrome; according to WHO classification
Notes	Power calculation performed: yes Intention-to-treat analysis performed: no

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: 'The subjects were randomly assigned...' 'To improve balance, the randomization of subjects to treatment was strati-

		fied for type of infertility (primary or secondary), IVF or ICSI, centre, and age.' Method not reported.
Allocation concealment?	Yes	Quote: '...by central remote allocation.'
Blinding? All outcomes	No	Open-label study
Incomplete outcome data addressed? All outcomes	No	No reasons for 14 withdrawals reported. Also unclear how many withdrawals per group
Free of selective reporting?	Yes	Data on all planned outcomes reported.
Free of other bias?	Unclear	No differences in baseline characteristics with regard to age, BMI, height and weight. Other characteristics reported in table, but no P values given

Salat-Baroux 1988

Methods	Parallel group study. Four study arms (A1+A2 and B1+B2), of which we can only include two study arms (A2 and B2) Number of women randomised: 42 (21 in study group (A2), 21 in control group (B2)) Number of withdrawals: 13 (eight in study group: three due to poorly followed treatment, one due to inadequate response, two due to spontaneous ovulation, two due to other reasons; five in control group: one due to ovarian cyst, four due to inadequate response) Number of women analysed: 29 Duration of study: seven months of recruitment
Participants	Country: authors are from France Inclusion criteria: infertile patients scheduled for IVF treatment, aged < 38 years Exclusion criteria: not reported Mean age and SD: Study group (A1+A2): 32.8 ± 0.7 Control group (B1+B2): 31.7 ± 0.5
Interventions	1) Progestogen (ethynodiol acetate) 2 mg twice daily for 11 to 17 days, start cycle day 15 + pure FSH four ampoules on post-treatment days six to seven and two ampoules on post-treatment days eight to nine + hMG (75 IU FSH + 75 IU LH) two ampoules on post-treatment days 10 to11 2) Pure FSH four ampoules on cycle days tow to three and two ampoules on cycle days four to five + hMG (75 IU FSH + 75 IU LH) when needed FSH and GnRH agonist are both continued until hCG injection (10,000 IU), administration depending on follicular maturity

Salat-Baroux 1988 (*Continued*)

Outcomes	Clinical pregnancy rate; not defined Pregnancy loss Day of hCG Values of E_2 and P on day of hCG Number of oocytes recovered, cleaved or replaced
Notes	Power calculation performed: no Intention-to-treat analysis performed: no

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	'Randomized', method not reported.
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	Reasons for 11 withdrawals reported. Reasons for 2 withdrawals unclear. Withdrawals due to inadequate response slightly imbalanced: 4 in control group, 1 in study group
Free of selective reporting?	Unclear	Planned outcomes not reported.
Free of other bias?	Unclear	Baseline characteristics reported in table, but no P values given. Data only reported on the total number of women in group A and the total in group B Slight differences in treatment protocol. Control group received hMG when needed, study group received hMG (2 ampoules) on day 10 and 11. In study group hCG was injected on day 12, in control group this day was variable

Shaker 1995

Methods	Parallel group study. Number of women randomised: 49 (number of women per group not reported; 22 cycles in study group, 29 cycles in control group) Number of withdrawals: 11 cycles (eight in control group: three due to conversion to IUI, one due to poor response, two due to failed fertilisation, two due to risk of OHS syndrome; three in study group: two due to poor response, one due to failure of embryo cleavage) Number of women analysed: unclear Duration of study: eight months of recruitment
Participants	Country: authors are from the United Kingdom Inclusion criteria: patients who underwent IVF treatment cycles and had an ovarian cyst > 15 mm in diameter or an endometrial thickness > 5 mm and serum E_2 concentration > 100 pmol/L after 14 days of GnRH agonist (buserelin acetate) treatment. Exclusion criteria: relevant uterine or ovarian pathology Mean age and SEM: Study group: 36.0 ± 0.86 Control group: 35.72 ± 0.69
Interventions	1) GnRH agonist (buserelin acetate) 500 μg daily start cycle day two or three + P (IM injection) 100 mg single dose on cycle day 16 or 17 + hMG, start when serum E_2 concentration $\leq$ 100 pmol/L 2) GnRH agonist (buserelin acetate) 500 μg daily, start cycle day 2 or 3 + hMG, start when serum E_2 concentration $\leq$ 100 pmol/L hMG start dose according to women's age, baseline serum FSH level, response to stimulation in previous treatment cycles hMG and GnRH agonist are both continued until hCG injection (10,000 IU), administered when 3 follicles $\geq$ 18 mm in diameter
Outcomes	Clinical pregnancy rate; not defined Serum E_2 levels on day of recruitment Number of days of hMG administration Number of days of GnRH agonist Endometrial thickness Mean diameter of ovarian cyst on day of recruitment and 6 days later Total number of hMG ampoules Number of follicles Number of oocytes retrieved Number of embryos transferred
Notes	Power calculation performed: no Intention-to-treat analysis performed: unclear

Risk of bias

Item	Authors' judgement	Description

Shaker 1995 (*Continued*)

Adequate sequence generation?	Yes	Quote: 'Randomization was done by drawing sequentially labelled sealed envelops, each containing a number obtained from a table of random numbers.'
Allocation concealment?	Yes	Sealed envelopes
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawals reported. two women in control were excluded due to risk of OHS syndrome, none in study group
Free of selective reporting?	Yes	Data on all planned outcomes reported.
Free of other bias?	No	Only number of cycles per treatment group known, number of women per group not reported. No significant differences in baseline characteristics between groups with regard to age, length of infertility, number of previous IVF cycles and cause of infertility. Data only reported on the number of cycles per group, not on the number of women

Tan 2001

Methods	Parallel group study. Number of women randomised: 117 (number of women per group not reported) Number of withdrawals: not reported Number of women analysed: unclear
Participants	Country: authors are from Canada Inclusion criteria: not reported Exclusion criteria: not reported Mean age and SD: not reported
Interventions	1) Progestogen (norethindrone) for five days, start cycle day one + GnRH agonist, start cycle day two. 2) GnRH agonist. Timing of treatment not reported.
Outcomes	Cyst formation Time required to achieve pituitary suppression Implantation rate Pregnancy rate

Tan 2001 (*Continued*)

Notes	Power calculation performed: unclear Intention-to-treat analysis used: unclear

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Unclear	No data reported
Free of selective reporting?	No	No data reported, especially no data on pregnancy rates.
Free of other bias?	Unclear	Unclear

Wang 2008

Methods	Academic, single centre, cross-over study. Crossover design: 20 women were treated with GnRH antagonist in the first cycle and with OCP + GnRH agonist in a second cycle. Number of women randomised: 121 (58 in study group, 63 in control group) Number of withdrawals: unclear Number of women analysed: unclear
Participants	Country: authors are from China Inclusion criteria: not reported Exclusion criteria: not reported Mean age and SD: Study group: 35.27 ± 4.76 Control group: 35.53 ± 4.21 Poor response: yes
Interventions	1) Combined OCP + GnRH agonist 2) GnRH antagonist Timing and dosage of treatments unclear.
Outcomes	Clinical pregnancy rate per embryo transfer; not defined Ampoules of gonadotrophins Time of Gn Number of oocytes retrieved Number of embryos transferred

Wang 2008 (*Continued*)

Notes	Power calculation performed: unclear Intention-to-treat analysis performed: unclear

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Unclear	No data reported
Free of selective reporting?	Unclear	No data reported
Free of other bias?	Unclear	Unclear

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

Study	Reason for exclusion
al-Mizyen 2000	No randomised controlled trial. Retrospective study.
Anderson 1990	No randomised controlled trial. The women only received controlled ovarian stimulation, but no embryo transfer as part of an ART cycle
Bellver 2007	No randomised controlled trial. Retrospective study.
Benadiva 1988	No randomised controlled trial.
Bendikson 2006	No randomised controlled trial. Retrospective study.
Biljan 1998b	No randomised controlled trial. Retrospective study. Each patient served as her own control
Branigan 1998	No randomised controlled trial. Each woman served as her own control
Brodt 1993	No randomised controlled trial. Single arm study.
Chung 2006	No randomised controlled trial. Retrospective study. Monophasic OCP versus triphasic OCP.

(*Continued*)

Cohen 1987	No randomised controlled trial.
Copperman 2003	No randomised controlled trial.
Couzinet 1995	No randomised controlled trial. Naltrexon used in treatment protocol
Cédrin-Durnerin 1995	No randomised controlled trial.
Damario 1997	No randomised controlled trial. Retrospective study.
Davy 2004	Compares different durations of combined OCP pre-treatment.
De Ziegler 1999	No randomised controlled trial. Open single-arm study.
Dickey 2001	No randomised controlled trial. Retrospective study.
Ditkoff 1997	No randomised controlled trial.
Doody 2001	No randomised controlled trial. The women in the study are oocyte donors. Compares different durations of combined OCP pre-treatment
Duvan 2008	No randomised controlled trial. Retrospective study.
Fanchin 2003b	No randomised controlled trial. Each woman served as her own control. The women only received controlled ovarian stimulation, but no embryo transfer as part of an ART cycle
Fisch 1996	No randomised controlled trial. Each woman served as her own control
Forman 1991	No randomised controlled trial.
Frederick 2004	No randomised controlled trial. Retrospective study.
Frydman 1986	No randomised controlled trial.
Galera 2004	No randomised controlled trial.
Gerli 1989	No randomised controlled trial. Single-arm study.
Godin 2003	No randomised controlled trial.
Gomez 2000	Compares two different ways of administration of oestrogen.
Gonen 1990	No randomised controlled trial. Clomiphene citrate used in treatment protocol
Gonzalez 1995	No randomised controlled trial. Retrospective study.
Hugues 1992	No randomised controlled trial. Single-arm study.

(*Continued*)

Jung 2000	Estrogen pre-treatment was not stopped before oocyte retrieval, but was also used as luteal phase support
Karande 2004	Compares two different ways of administration of a combined contraceptive (Nuvaring versus oral Desogen)
Keltz 2007	No randomised controlled trial. Retrospective study.
Kovacs 2001	No randomised controlled trial. Retrospective study.
Leondires 1999	No randomised controlled trial. Retrospective study.
Letterie 2000	Women only received a combination of an oestrogen and a progestogen, but no gonadotrophins or GnRH analogues as part of an ART cycle. Compares two different timings of administration
Lewin 2002	Compares two different doses of oestrogen treatment for endometrial preparation
Lindheim 1996	No randomised controlled trial.
Loutradis 2003	No randomised controlled trial. Retrospective study.
Martinez 2006	The women in the study are oocyte donors.
Mashiach 1989	Compares different durations of combined OCP pre-treatment.
Meldrum 2002	No randomised controlled trial. Open-label single-arm study.
Meldrum 2008	No randomised controlled trial. Open-label single-arm study.
Min 2005	No randomised controlled trial. Retrospective study.
Mirkin 2003	No randomised controlled trial. Retrospective study.
Mulangi 1997	No randomised controlled trial. Each patient served as her own control
Neal 1993	No randomised controlled trial.
Pados 1995	No randomised controlled trial. Retrospective study. Pednisolon used in treatment protocol.
Palomba 2008	No randomised controlled trial.
Pinkas 2008	No randomised controlled trial. Retrospective study.
Ramsewak 2005	No randomised controlled trial. Retrospective study.
Russell 1997	Compares different doses and timings of oestrogen pre-treatments
Sanghvi 2002	No randomised controlled trial. Retrospective study. Single-arm study

(*Continued*)

Schoolcraft 1997	No randomised controlled trial.
Steinkampf 1991	Women only received ovulation induction, no embryo transfer as part of an ART cycle
Surrey 1989	No randomised controlled trial.
Surrey 1998	No randomised controlled trial. Each woman served as her own control
Talebian 2004	No randomised controlled trial. Retrospective study.
Talebian 2007	No randomised controlled trial. Retrospective study.
Tarlatzis 1993	No randomised controlled trial.
Tartagni 2007	The patients in the study are women with premature ovarian failure
Weisman 1989	No randomised controlled trial.
Yokota 2006	No randomised controlled trial.
Yoshida 2005	No randomised controlled trial. Retrospective study.
Zhao 2008	No randomised controlled trial. Retrospective study.

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

Tavmergen 2009

Methods	RCT
Participants	422 women
Interventions	Two armed study either pre treatment or not with 200IU recFSH in a GnRH antagonist protocol
Outcomes	Ongoing pregnancy
Notes	

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

Organon 2008

Trial name or title	A randomised, open-label clinical trial to identify predictive factors for controlled ovarian stimulation using a fixed daily dose of 200 IU recombinant FSH in GnRH antagonist regimen with or without oral contraceptive scheduling
Methods	Randomised controlled trial
Participants	Inclusion criteria: (i) females of couples with an indication for IVF and/or ICSI scheduled for their first COS treatment cycle; (ii) >18 and ≤ 39 years of age at the time of signing informed consent; (iii) BMI ≤ 32 kg/m^2; (iv) normal menstrual cycle length of 24 to 35 days; and (v) availability of ejaculatory sperm (use of donated and/or cryopreserved sperm is allowed). Exclusion criteria: (i) (history of) endocrine abnormality; (ii) < two ovaries or any other ovarian abnormality (e. g. > 10 mm endometrioma); (iii) presence of unilateral or bilateral hydrosalpinx; (iv) presence of any clinically relevant pathology affecting the uterine cavity or fibroids ≥ five cm; (v) history of ≥ three miscarriages; (vi) FSH or LH > 12 IU/L during the early follicular phase; (vii) any clinically relevant abnormal laboratory value (FSH, LH, E2, P, total T, prolactin, TSH, blood biochemistry, hematology and urinalysis) based on a sample during the screening phase; (viii) contraindications for the use of gonadotrophins (tumours, pregnancy, lactation, undiagnosed vaginal bleeding, hypersensitivity, ovarian cysts); (ix) contraindications for the use of oral contraceptive pills (thromboembolism, breast cancer, undiagnosed vaginal bleeding); (x) (recent history of) epilepsy, HIV infection, diabetes, cardiovascular, gastrointestinal, hepatic, renal or pulmonary disease; (xi) abnormal karyotyping of the patient or her partner (if karyotyping is performed); (xii) (history of) alcohol or drug abuse within 12 months of signing the consent; (xiii) use of hormonal preparations within one month prior to randomization; (xiv) hypersensitivity to any of the concomitant medication; and (xv) administration of investigational drugs within three months prior to signing the informed consent
Interventions	1) combined OCP (Desogen) for one month + ovarian stimulation 2) ovarian stimulation
Outcomes	Primary: total number of oocytes Secondary: number of mature oocytes, number of follicles on stimulation day 8, number of follicles on day of hCG, number of fertilised (2PN) oocytes, number of good quality embryos, cycle cancellation rate
Starting date	October 2006
Contact information	Dr. Z. Rosenwaks
Notes	Sponsored by Organon/Schering Plough

DATA AND ANALYSES

Comparison 1. Combined OCP versus no Rx

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live births	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 COCP + Ant vs Ant	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.11, 1.74]
1.2 COCP + Ant vs Ag	1	182	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.48, 2.10]
1.3 COCP + Ant vs Ant, low response	1	54	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.82 [0.53, 6.25]
1.4 COCP + Ant vs Ag, low response	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.46, 5.09]
2 Ongoing pregnancies	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 COCP + Ant vs Ant	4	847	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.53, 1.03]
2.2 COCP + Ant vs Ag	2	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.47, 1.23]
2.3 COCP + Ant vs Ant, low response	1	54	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.82 [0.53, 6.25]
2.4 COCP + Ant vs Ag, low response	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.46, 5.09]
3 Clinical/ongoing pregnancies	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 COCP + Ag vs Ag	1	102	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.53, 2.66]
3.2 COCP + Ant vs Ant	4	847	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.50, 0.96]
3.3 COCP + Ant vs Ag	3	472	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.53, 1.26]
3.4 COCP + Ant vs Ant, low response	1	54	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [0.53, 5.60]
3.5 COCP + Ant vs Ag, low response	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.47, 4.71]
3.6 COCP + Ag vs Ant, low response	1	121	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.56, 2.53]
4 Oocytes retrieved	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 COCP + Ant vs Ant	5	891	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.55, 1.01]
4.2 COCP + Ant vs Ag	3	440	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-1.54, 1.53]
4.3 COCP + Ant vs Ant, low response	1	54	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.61, 1.41]
4.4 COCP + Ant vs Ag, low response	1	55	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.98, 1.18]
4.5 COCP + Ag vs Ant, low response	1	110	Mean Difference (IV, Fixed, 95% CI)	-1.01 [-1.91, -0.11]
5 Days of gonadotrophin treatment	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 COCP + Ant vs Ant	3	689	Mean Difference (IV, Fixed, 95% CI)	1.44 [1.15, 1.72]
5.2 COCP + Ant vs Ag	3	434	Mean Difference (IV, Fixed, 95% CI)	0.51 [0.17, 0.84]
5.3 COCP + Ant vs Ant, low response	1	54	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.45, 1.05]
5.4 COCP + Ant vs Ag, low response	1	55	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.42, -0.78]

5.5 COCP + Ag vs Ant, low response	1	110	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.70, 0.60]
6 Amount of gonadotrophins administered	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 COCP + Ant vs Ant	4	734	Mean Difference (IV, Fixed, 95% CI)	231.14 [161.50, 300.78]
6.2 COCP + Ant vs Ag	2	385	Mean Difference (IV, Fixed, 95% CI)	209.52 [61.16, 357.87]
6.3 COCP + Ant vs Ant, low response	1	54	Mean Difference (IV, Fixed, 95% CI)	32.40 [-207.04, 271.84]
6.4 COCP + Ant vs Ag, low response	1	55	Mean Difference (IV, Fixed, 95% CI)	-426.30 [-657.90, -194.70]
7 Pregnancy losses	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 COCP + Ant vs Ant	4	847	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.76, 2.12]
7.2 COCP + Ant vs Ag	3	472	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.24, 1.10]
7.3 COCP + Ant vs Ant, low response	1	54	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.06, 16.42]
7.4 COCP + Ant vs Ag, low response	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.06, 17.04]
8 Ovarian cyst formation	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 COCP + Ag vs Ag	1	102	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.07 [0.03, 0.16]
8.2 COCP + Ant vs Ant	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.09, 2.57]
9 Multiple pregnancies	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 COCP + Ant vs Ant	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [0.23, 23.65]
9.2 COCP + Ant vs Ag	2	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.37, 2.82]
9.3 COCP + Ant vs Ant, low response	1	54	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.00 [0.20, 20.08]
9.4 COCP + Ant vs Ag, low response	1	55	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [0.21, 20.84]
10 OHS syndrome	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 COCP + Ant vs Ant	1	234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.26, 8.80]
10.2 COCP + Ant vs Ag	2	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.21, 1.92]

Comparison 2. Progestogen versus placebo/ no Rx

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live births	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Prog + Ag vs Ag	2	222	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.69, 2.62]
1.2 Prog + Ant vs Ant	1	47	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.19, 2.50]
2 Ongoing pregnancies	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Prog + Ag vs Ag	1	105	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.46, 2.95]
2.2 Prog + Ant vs Ant	1	47	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.19, 2.50]
2.3 Prog + Gon vs Gon	1	42	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.10, 4.06]
3 Clinical pregnancies	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Prog + Ag vs Ag	3	374	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [1.20, 3.17]
3.2 Prog + Ant vs Ant	1	47	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.17, 1.69]
3.3 Prog + Gon vs Gon	1	42	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.14, 3.56]

4 Oocytes retrieved	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Prog + Ag vs Ag	2	210	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-2.13, 1.01]
4.2 Prog + Ant vs Ant	1	47	Mean Difference (IV, Fixed, 95% CI)	2.70 [-0.98, 6.38]
4.3 Prog + Gon vs Gon	1	29	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Days of gonadotrophin treatment	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Prog + Ag vs Ag	2	210	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.35, 0.50]
6 Amount of gonadotrophins administered	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Prog + Ant vs Ant	1	47	Mean Difference (IV, Fixed, 95% CI)	276.0 [-75.53, 627.53]
7 Pregnancy losses	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Prog + Ag vs Ag	2	222	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.17 [0.71, 6.69]
7.2 Prog + Ant vs Ant	1	47	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.08, 1.92]
7.3 Prog + Gon vs Gon	1	42	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.06, 16.55]
8 Ovarian cyst formation	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Prog + Ag vs Ag	3	374	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.12, 0.35]
9 Multiple pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Prog + Ant vs Ant	1	47	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.06, 17.23]

Comparison 3. Estrogen versus no Rx

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live births	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Estr + Ant vs Ant	1	49	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.09, 1.41]
1.2 Estr + Ant vs Ag	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.13, 6.53]
2 Ongoing pregnancies	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Estr + Ant vs Ant	1	49	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.09, 1.41]
2.2 Estr + Ant vs Ag	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.13, 6.53]
3 Clinical pregnancies	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Estr + Ant vs Ant	2	139	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.38, 1.62]
3.2 Estr + Ant vs Ag	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.13, 6.53]
4 Oocytes retrieved	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Estr + Ant vs Ant	2	136	Mean Difference (IV, Fixed, 95% CI)	2.01 [1.76, 2.25]
4.2 Estr + Ant vs Ag	1	20	Mean Difference (IV, Fixed, 95% CI)	0.40 [-4.61, 5.41]
5 Days of gonadotrophin treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Estr + Ant vs Ag	1	20	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-4.10, -0.90]
6 Amount of gonadotrophins administered	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Estr + Ant vs Ant	2	136	Mean Difference (IV, Fixed, 95% CI)	207.08 [167.77, 246.39]
6.2 Estr + Ant vs Ag	1	20	Mean Difference (IV, Fixed, 95% CI)	-16.0 [-478.88, 446.88]
7 Pregnancy losses	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Estr + Ant vs Ant	1	49	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.04, 1.17]
7.2 Estr + Ant vs Ag	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

8 Ovarian cyst formation	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Estr + Ant vs Ag	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
9 Multiple pregnancies	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Estr + Ant vs Ant	1	49	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.55]
9.2 Estr + Ant vs Ag	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.52 [0.20, 101.00]
10 OHS syndrome	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 Estr + Ant vs Ag	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Comparison 4. Combined OCP versus progestogen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live births	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 COCP + Ant vs Prog + Ant	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.13, 2.79]
2 Ongoing pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 COCP + Ant vs Prog + Ant	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.13, 2.79]
3 Clinical pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 COCP + Ant vs Prog + Ant	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.19, 2.68]
4 Oocytes retrieved	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 COCP + Ant vs Prog + Ant	1	44	Mean Difference (IV, Fixed, 95% CI)	1.40 [-3.24, 6.04]
5 Amount of gonadotrophins administered	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 COCP + Ant vs Prog + Ant	1	44	Mean Difference (IV, Fixed, 95% CI)	164.0 [-249.03, 577.03]
6 Pregnancy losses	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 COCP + Ant vs Prog + Ant	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.14, 8.43]
7 Multiple pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 COCP + Ant vs Prog + Ant	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.22 [0.22, 22.56]

Comparison 5. Combined OCP versus estrogen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live births	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 COCP + Ant vs Estr + Ant	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.22, 6.69]
2 Ongoing pregnancies	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 COCP + Ant vs Estr + Ant	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.22, 6.69]
2.2 COCP + Ag vs Estr + Ant	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.03, 0.70]
3 Clinical pregnancies	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

3.1 COCP + Ant vs Estr + Ant	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.62 [0.38, 6.90]
3.2 COCP + Ag vs Estr + Ant	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.03, 0.80]
4 Oocytes retrieved	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 COCP + Ant vs Estr + Ant	1	43	Mean Difference (IV, Fixed, 95% CI)	0.90 [-3.70, 5.50]
5 Amount of gonadotrophins administered	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 COCP + Ant vs Estr + Ant	1	43	Mean Difference (IV, Fixed, 95% CI)	474.0 [95.10, 852.90]
6 Pregnancy losses	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 COCP + Ant vs Estr + Ant	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.43 [0.24, 24.79]
6.2 COCP + Ag vs Estr + Ant	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.06, 18.49]
7 Multiple pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 COCP + Ant vs Estr + Ant	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.40 [0.56, 156.66]

Comparison 6. Progestogen versus estrogen

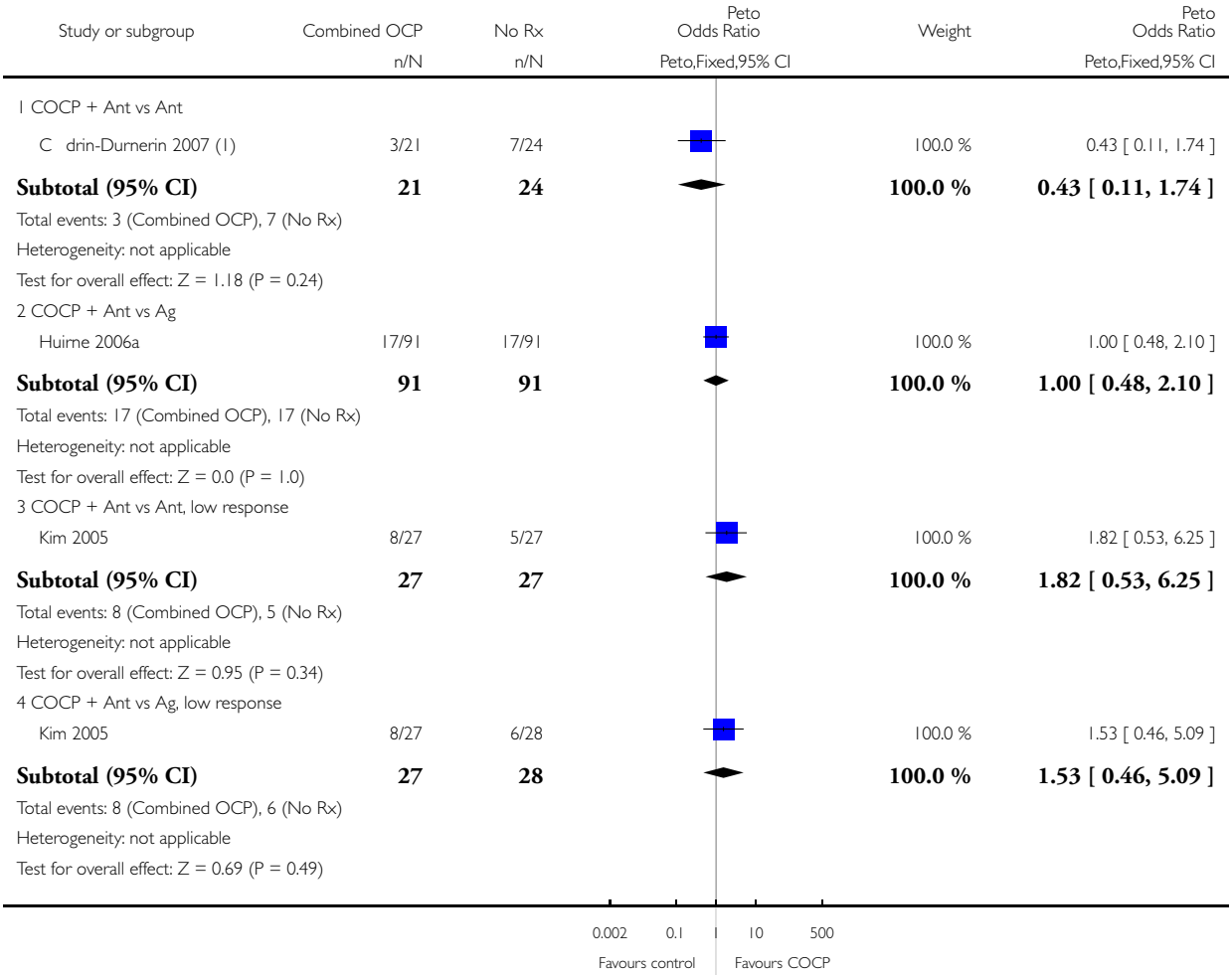
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live births	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Prog + Ant vs Estr + Ant	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [0.44, 8.94]
2 Ongoing pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Prog + Ant vs Estr + Ant	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [0.44, 8.94]
3 Clinical pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Prog + Ant vs Estr + Ant	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.23 [0.59, 8.44]
4 Oocytes retrieved	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Prog + Ant vs Estr + Ant	1	45	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-4.68, 3.68]
5 Amount of gonadotrophins administered	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Prog + Ant vs Estr + Ant	1	45	Mean Difference (IV, Fixed, 95% CI)	310.0 [-40.60, 660.60]
6 Pregnancy losses	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Prog + Ant vs Estr + Ant	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.19 [0.22, 22.19]
7 Multiple pregnancies	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Prog + Ant vs Estr + Ant	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.06 [0.16, 407.60]

Analysis 1.1. Comparison 1 Combined OCP versus no Rx, Outcome 1 Live births.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 1 Live births



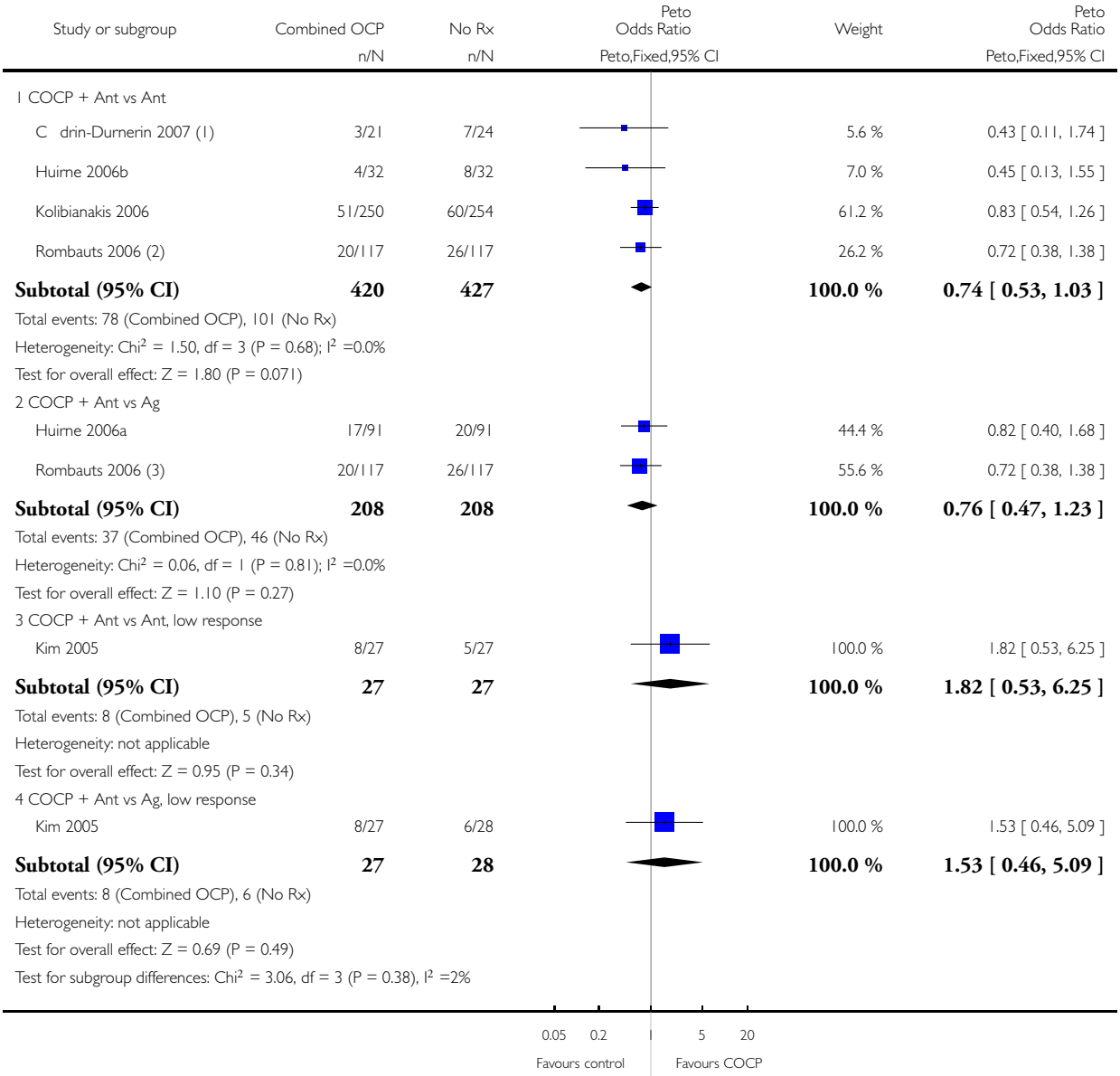
(1) Data obtained from Dr. Griesinger.

Analysis 1.2. Comparison 1 Combined OCP versus no Rx, Outcome 2 Ongoing pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 2 Ongoing pregnancies



(1) Data obtained from Dr. C drin-Durnerin.

(2) Includes 2 spontaneous pregnancies in the study group and 3 in the control group.

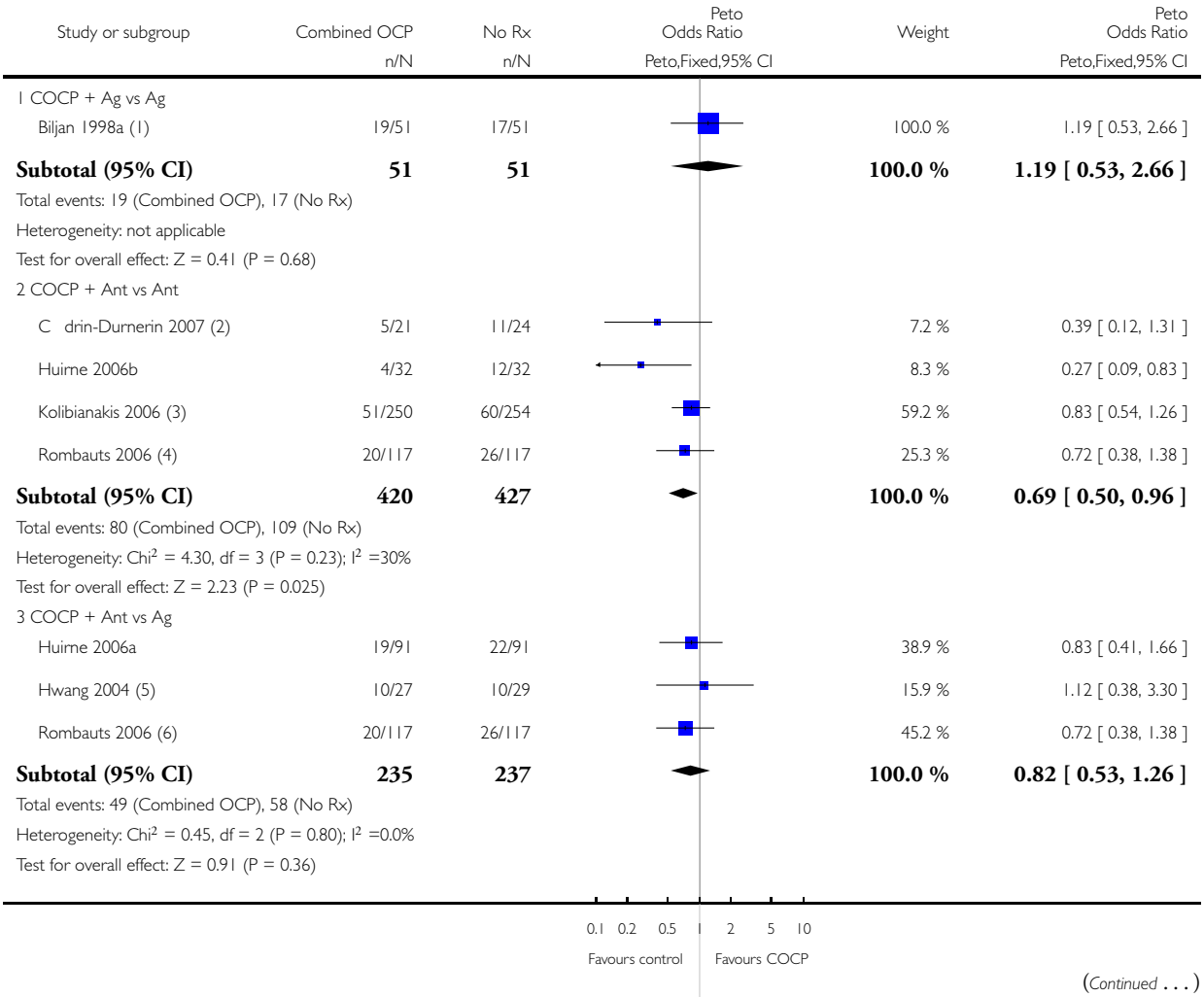
(3) Includes 2 spontaneous pregnancies in the study group.

Analysis 1.3. Comparison 1 Combined OCP versus no Rx, Outcome 3 Clinical/ongoing pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 3 Clinical/ongoing pregnancies



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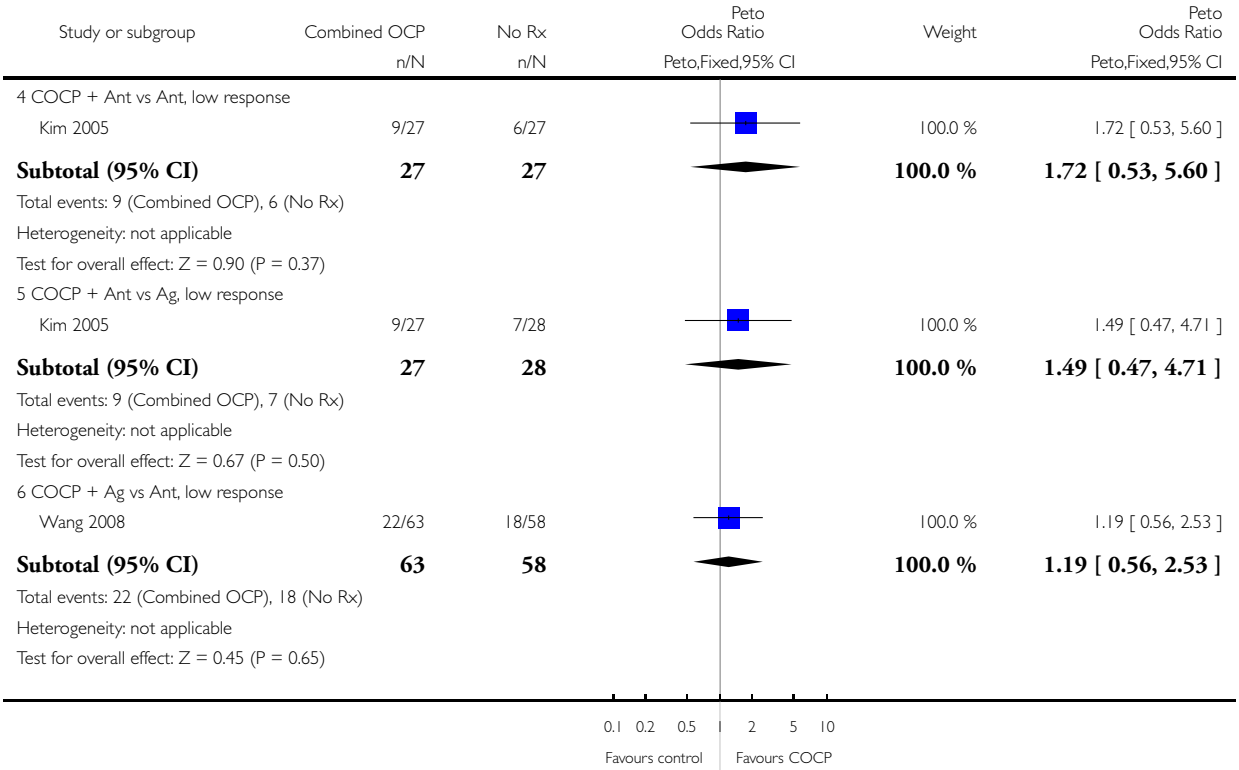


(1) Numbers calculated from rates; Number of women per group unknown, only number of cycles known.

(2) Data obtained from Dr. C drin-Durnerin.

(3) Ongoing pregnancies.

(4) Ongoing pregnancies. Includes 2 spontaneous pregnancies in the study group and 3 in the control group.

(5) Calculated from rates.

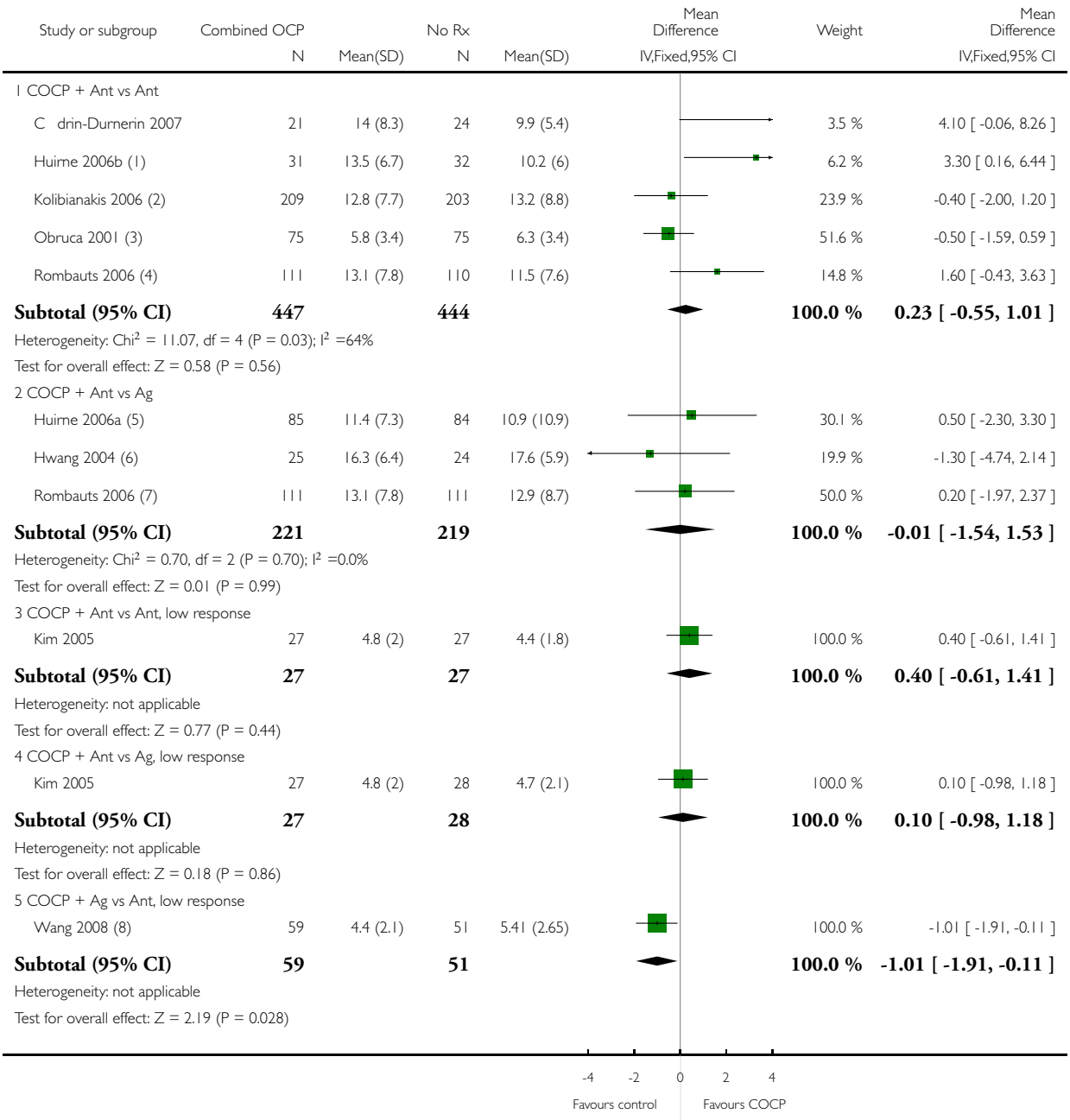
(6) Ongoing pregnancies. Includes 2 spontaneous pregnancies in the study group.

Analysis 1.4. Comparison 1 Combined OCP versus no Rx, Outcome 4 Oocytes retrieved.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 4 Oocytes retrieved



(1) No ITT in COCP group.

(2) No ITT. 'Cumulus oocyte complexes'.

(3) Unsure about ITT.

(4) No ITT.

(5) No ITT.

(6) No ITT.

(7) No ITT.

(8) No ITT.

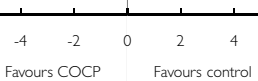
Analysis 1.5. Comparison 1 Combined OCP versus no Rx, Outcome 5 Days of gonadotrophin treatment.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 5 Days of gonadotrophin treatment

Study or subgroup	Combined OCP N	Mean(SD)	No Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 COCP + Ant vs Ant							
Huirne 2006b (1)	31	11.6 (2.1)	32	8.7 (1.6)		9.4 %	2.90 [1.98, 3.82]
Kolibianakis 2006 (2)	209	9.7 (2)	203	9.1 (2)		54.0 %	0.60 [0.21, 0.99]
Rombauts 2006 (3)	109	11.7 (1.9)	105	9.4 (1.6)		36.5 %	2.30 [1.83, 2.77]
Subtotal (95% CI)	**349**		**340**			**100.0 %**	**1.44 [1.15, 1.72]**
Heterogeneity: Chi^2 = 40.62, df = 2 (P<0.00001); I^2 =95%							
Test for overall effect: Z = 9.92 (P < 0.00001)							
2 COCP + Ant vs Ag							
Huirne 2006a (4)	90	10.1 (1.8)	85	10.3 (1.6)		44.5 %	-0.20 [-0.70, 0.30]
Hwang 2004 (5)	25	9.9 (2.1)	24	10.8 (2.2)		7.8 %	-0.90 [-2.11, 0.31]
Rombauts 2006 (6)	109	11.7 (1.9)	101	10.3 (1.7)		47.7 %	1.40 [0.91, 1.89]
Subtotal (95% CI)	**224**		**210**			**100.0 %**	**0.51 [0.17, 0.84]**
Heterogeneity: Chi^2 = 25.71, df = 2 (P<0.00001); I^2 =92%							
Test for overall effect: Z = 2.96 (P = 0.0030)							
3 COCP + Ant vs Ant, low response							



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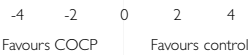
Study or subgroup	Combined OCP N	Mean(SD)	No Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kim 2005	27	10 (1.4)	27	9.7 (1.4)		100.0 %	0.30 [-0.45, 1.05]
Subtotal (95% CI)	**27**		**27**			**100.0 %**	**0.30 [-0.45, 1.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.79 (P = 0.43)							
4 COCP + Ant vs Ag, low response							
Kim 2005	27	10 (1.4)	28	11.6 (1.7)		100.0 %	-1.60 [-2.42, -0.78]
Subtotal (95% CI)	**27**		**28**			**100.0 %**	**-1.60 [-2.42, -0.78]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.82 (P = 0.00014)							
5 COCP + Ag vs Ant, low response							
Wang 2008	59	9.6 (1.9)	51	9.65 (1.6)		100.0 %	-0.05 [-0.70, 0.60]
Subtotal (95% CI)	**59**		**51**			**100.0 %**	**-0.05 [-0.70, 0.60]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.15 (P = 0.88)							
Test for subgroup differences: Chi^2 = 63.07, df = 4 (P = 0.00), I^2 =94%							



(1) No ITT in COCP group.

(2) No ITT. Data obtained from Dr. Griesinger.

(3) No ITT.

(4) No ITT.

(5) No ITT.

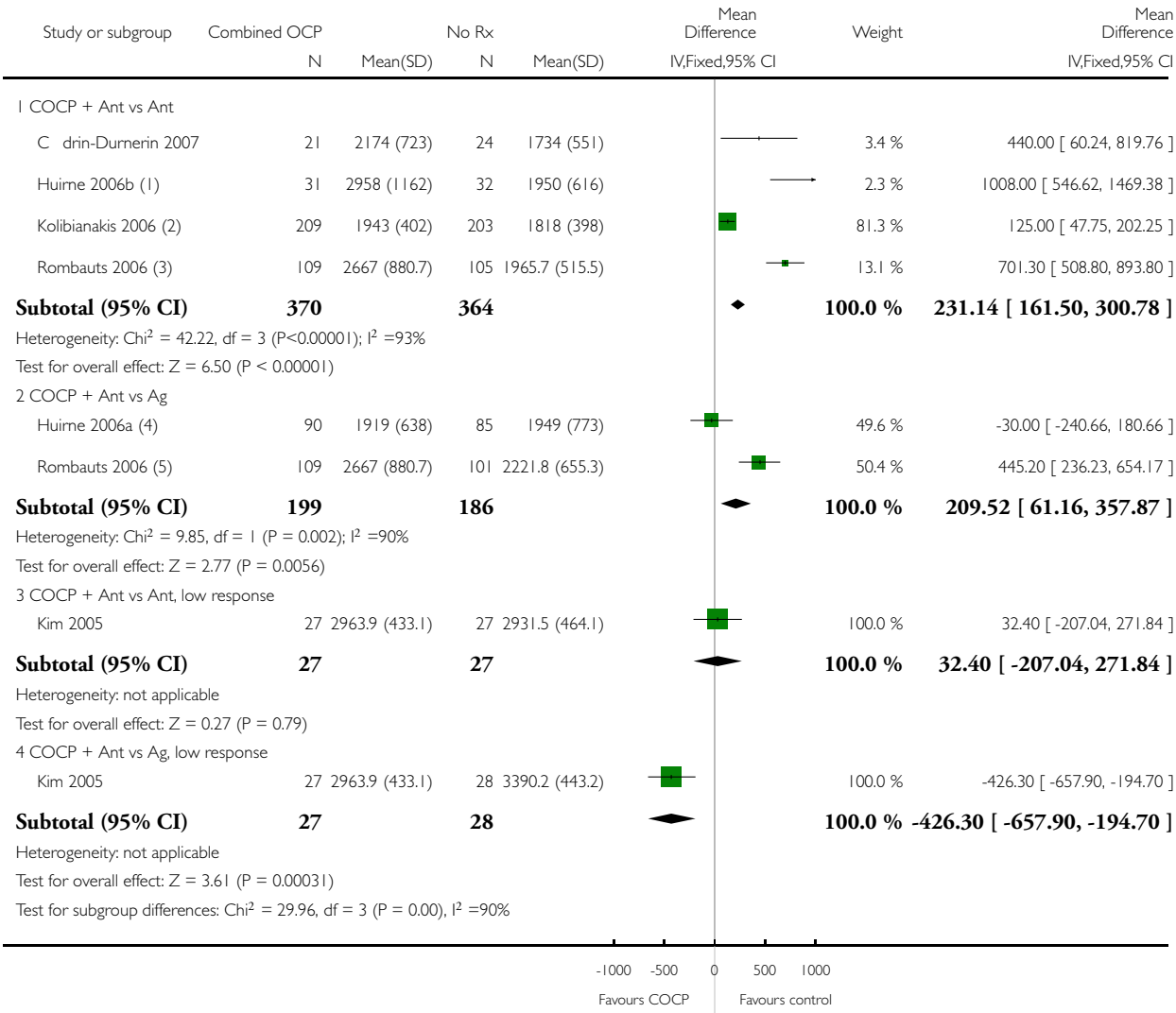
(6) No ITT.

Analysis 1.6. Comparison 1 Combined OCP versus no Rx, Outcome 6 Amount of gonadotrophins administered.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 6 Amount of gonadotrophins administered



(1) No ITT in COCP group.

(2) No ITT. Data obtained from Dr. Griesinger.

(3) No ITT.

(4) No ITT.

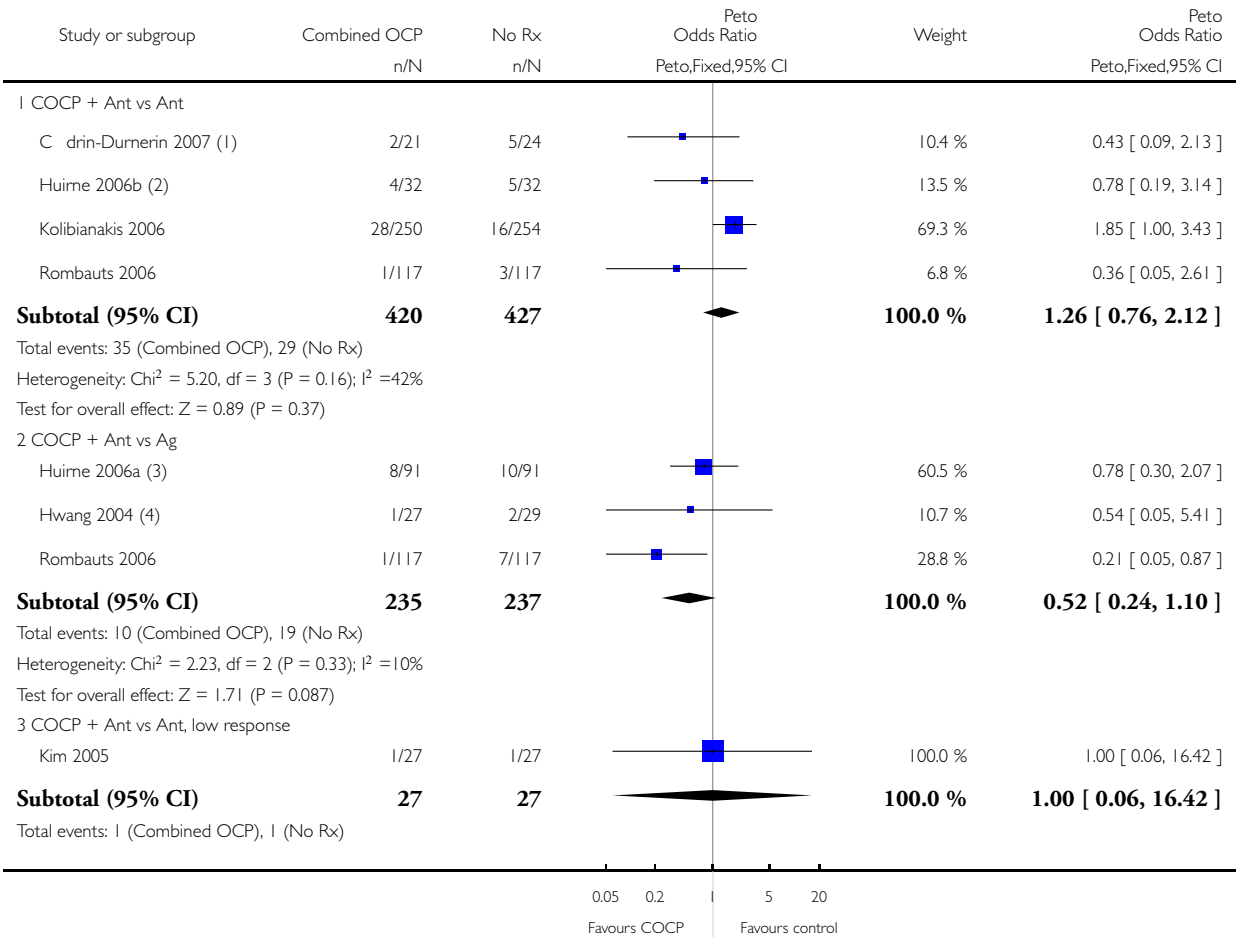
(5) No ITT.

Analysis 1.7. Comparison 1 Combined OCP versus no Rx, Outcome 7 Pregnancy losses.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 7 Pregnancy losses



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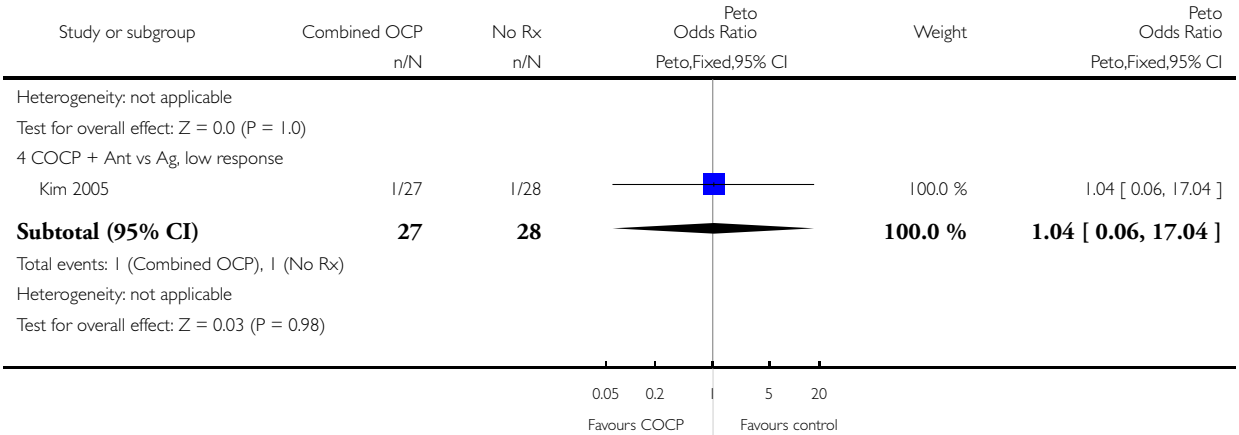


(1) Calculated from the number of clinical pregnancies minus the number of live births.

(2) Calculated from the number of positive pregnancy tests minus the number of ongoing pregnancies.

(3) Calculated from the number of positive pregnancy tests minus the number of live births.

(4) Calculated from rates.

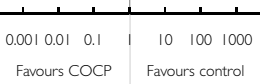
Analysis 1.8. Comparison 1 Combined OCP versus no Rx, Outcome 8 Ovarian cyst formation.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 8 Ovarian cyst formation

Study or subgroup	Combined OCP n/N	No Rx n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 COCP + Ag vs Ag					
Biljan 1998a (1)	0/51	27/51		100.0 %	0.07 [0.03, 0.16]
Subtotal (95% CI)	**51**	**51**		**100.0 %**	**0.07 [0.03, 0.16]**
Total events: 0 (Combined OCP), 27 (No Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.03 (P < 0.00001)					
2 COCP + Ant vs Ant					
Huirne 2006b	2/32	4/32		100.0 %	0.48 [0.09, 2.57]
Subtotal (95% CI)	**32**	**32**		**100.0 %**	**0.48 [0.09, 2.57]**
Total events: 2 (Combined OCP), 4 (No Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					



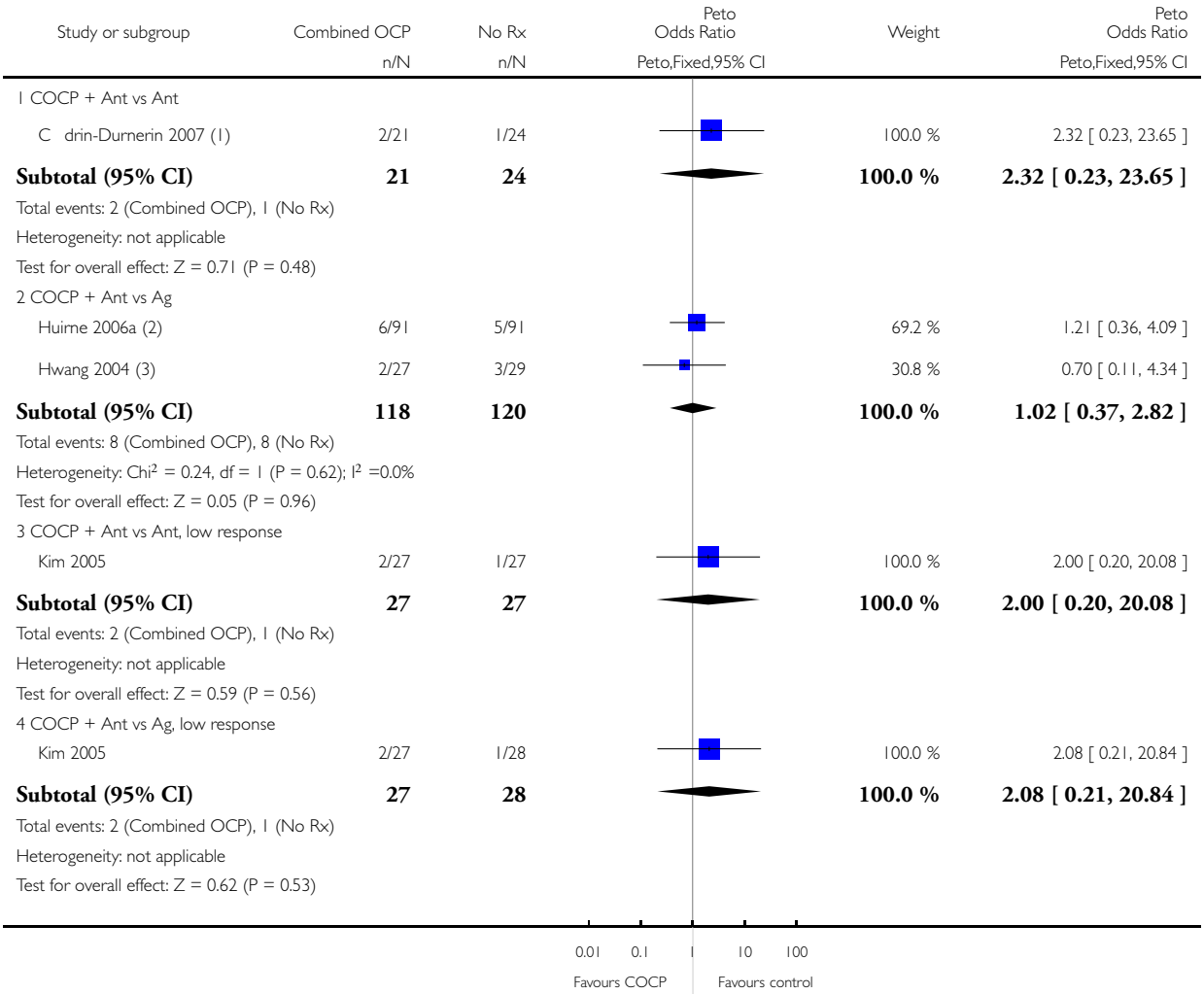
(1) Number of women per group unknown, only number of cycles known.

Analysis 1.9. Comparison 1 Combined OCP versus no Rx, Outcome 9 Multiple pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 9 Multiple pregnancies



(1) Data obtained from Dr. Griesinger.

(2) 'Multiple clinical pregnancies'.

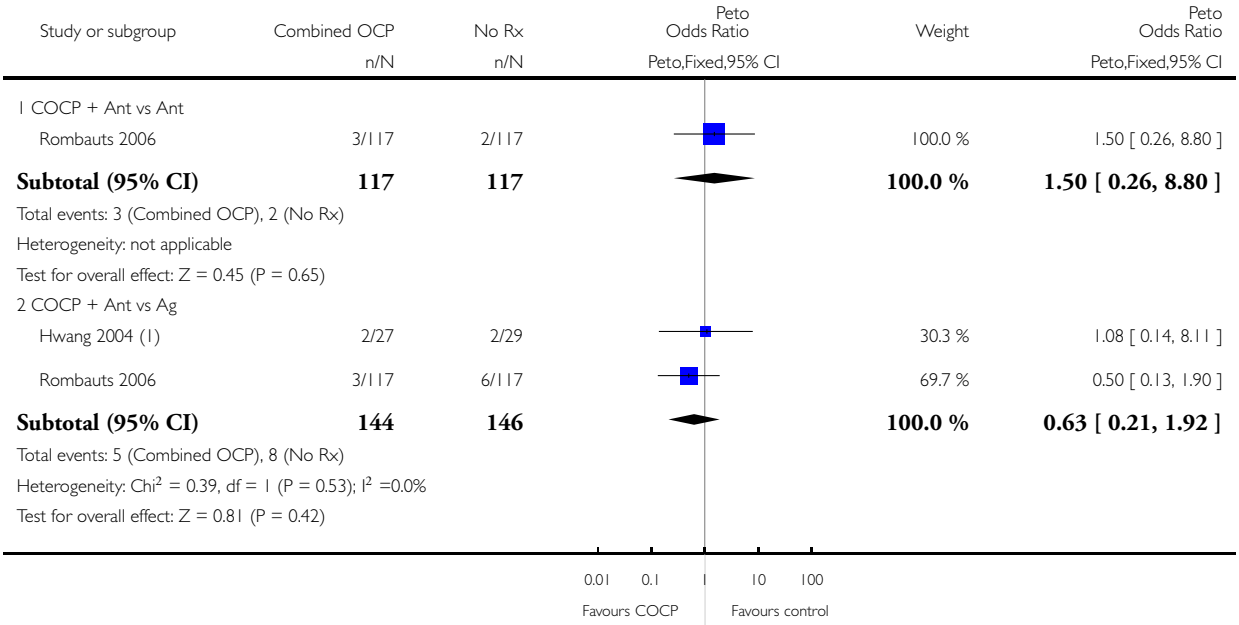
(3) Data obtained from text. In the study group 2 ongoing. In the control group 1 live birth and 2 ongoing.

Analysis 1.10. Comparison 1 Combined OCP versus no Rx, Outcome 10 OHS syndrome.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 1 Combined OCP versus no Rx

Outcome: 10 OHS syndrome



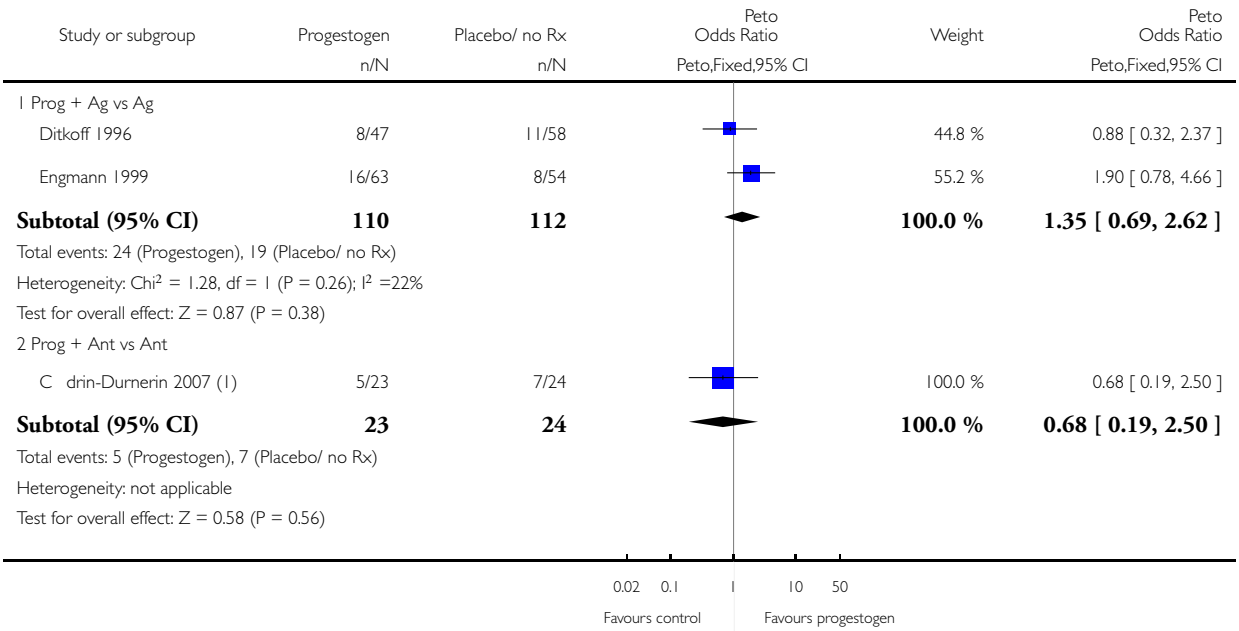
(1) Calculated from rates.

Analysis 2.1. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 1 Live births.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 1 Live births



(1) Data obtained from Dr. Griesinger.

Analysis 2.2. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 2 Ongoing pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 2 Ongoing pregnancies

Study or subgroup	Progestogen n/N	Placebo/ no Rx n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Prog + Ag vs Ag					
Ditkoff 1996 (1)	11/47	12/58		100.0 %	1.17 [0.46, 2.95]
Subtotal (95% CI)	**47**	**58**		**100.0 %**	**1.17 [0.46, 2.95]**
Total events: 11 (Progestogen), 12 (Placebo/ no Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 Prog + Ant vs Ant					
C drin-Durnerin 2007	5/23	7/24		100.0 %	0.68 [0.19, 2.50]
Subtotal (95% CI)	**23**	**24**		**100.0 %**	**0.68 [0.19, 2.50]**
Total events: 5 (Progestogen), 7 (Placebo/ no Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
3 Prog + Gon vs Gon					
Salat-Baroux 1988 (2)	2/21	3/21		100.0 %	0.64 [0.10, 4.06]
Subtotal (95% CI)	**21**	**21**		**100.0 %**	**0.64 [0.10, 4.06]**
Total events: 2 (Progestogen), 3 (Placebo/ no Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					

(1) Data obtained from Dr. Ditkoff.

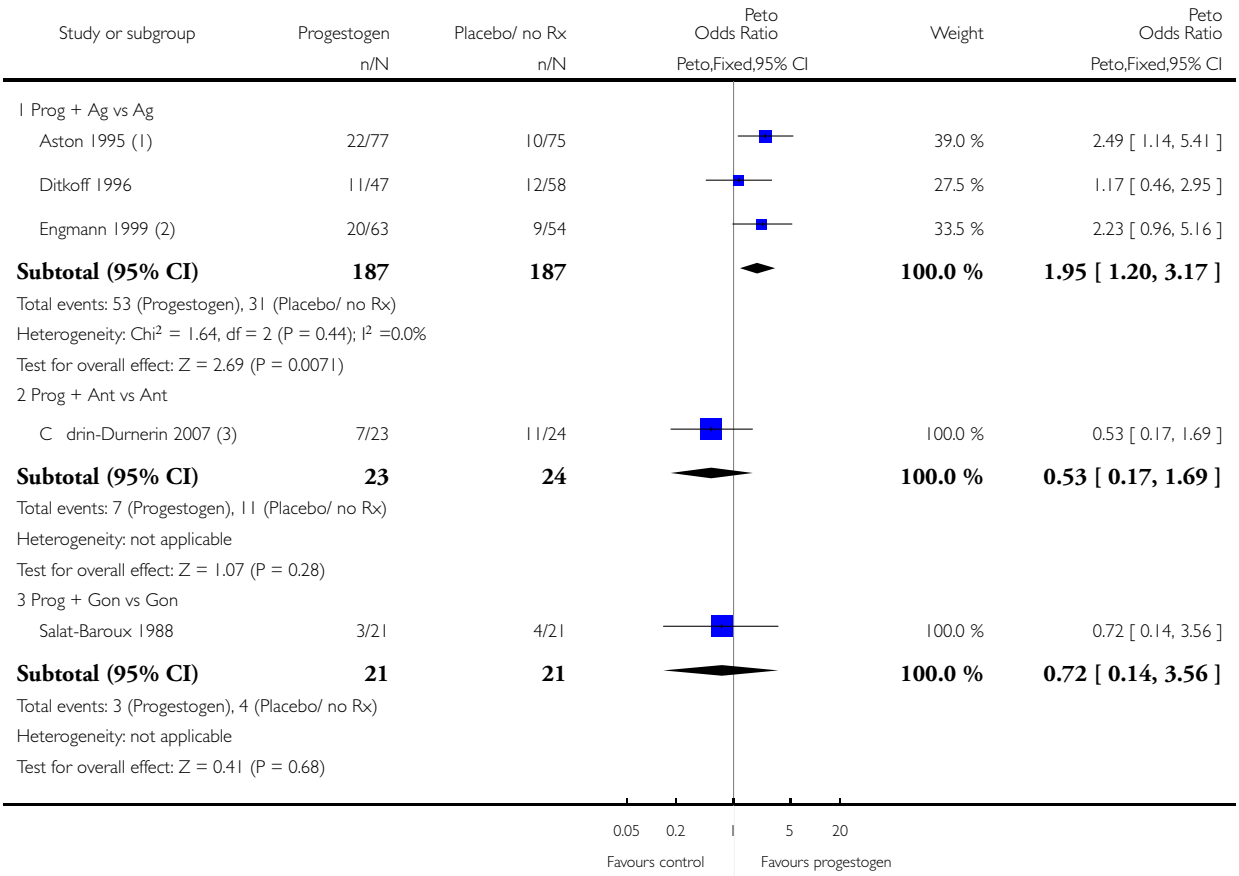
(2) Data obtained from text.

Analysis 2.3. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 3 Clinical pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 3 Clinical pregnancies



(1) Numbers calculated from rates.

(2) Positive pregnancy test.

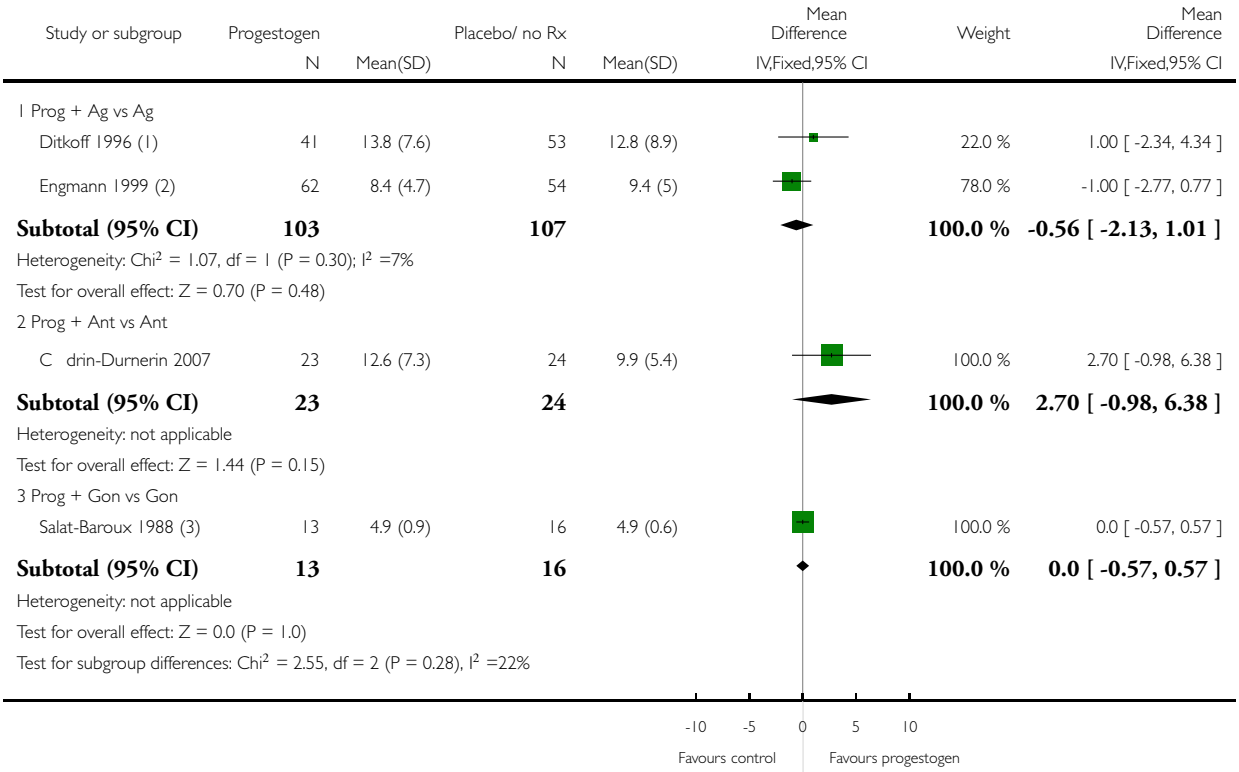
(3) Data obtained from Dr. C drin-Durnerin.

Analysis 2.4. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 4 Oocytes retrieved.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 4 Oocytes retrieved



(1) No ITT.

(2) No ITT in progestogen group. 'Mature oocytes'.

(3) No ITT.

Analysis 2.5. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 5 Days of gonadotrophin treatment.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 5 Days of gonadotrophin treatment

Study or subgroup	Progestogen N	Mean(SD)	Placebo/ no Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Prog + Ag vs Ag							
Ditkoff 1996 (1)	41	11.8 (1.5)	53	11.1 (1.5)		48.0 %	0.70 [0.09, 1.31]
Engmann 1999 (2)	62	11.2 (1.5)	54	11.7 (1.7)		52.0 %	-0.50 [-1.09, 0.09]
Subtotal (95% CI)	**103**		**107**			**100.0 %**	**0.08 [-0.35, 0.50]**

Heterogeneity: Chi^2 = 7.69, df = 1 (P = 0.01); I^2 =87%

Test for overall effect: Z = 0.35 (P = 0.73)

Test for subgroup differences: Not applicable

(1) No ITT.

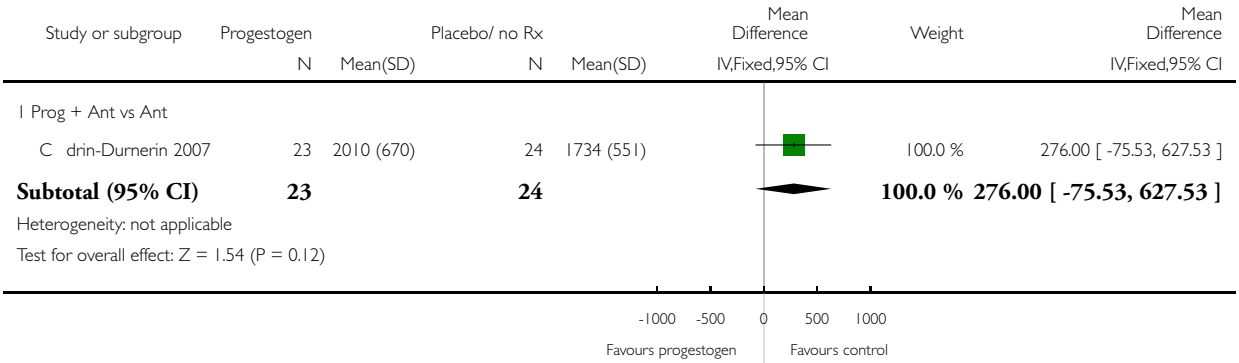
(2) No ITT in progestogen group.

Analysis 2.6. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 6 Amount of gonadotrophins administered.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 6 Amount of gonadotrophins administered

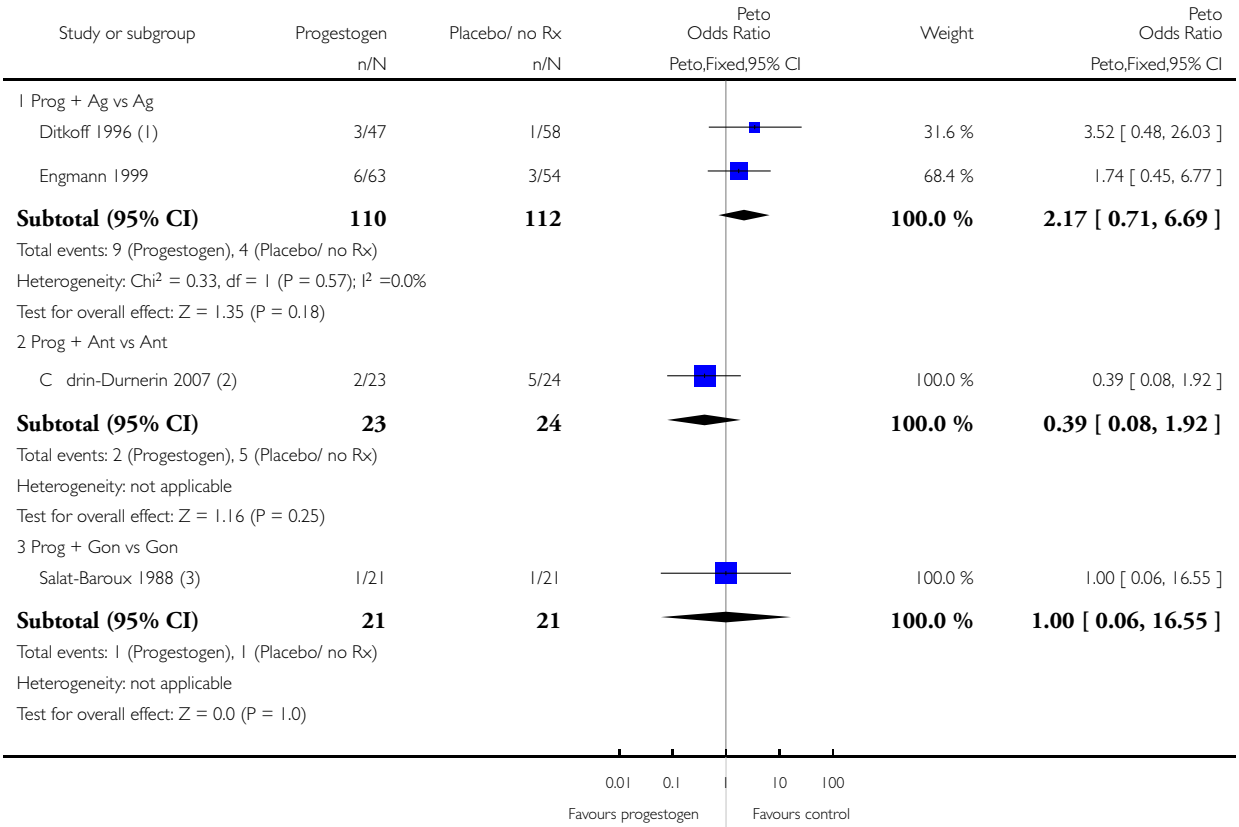


Analysis 2.7. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 7 Pregnancy losses.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 7 Pregnancy losses



(1) Calculated from the number of clinical pregnancies minus the number of live births.

(2) Calculated from the number of clinical pregnancies minus the number of live births.

(3) Data obtained from text, not sure whether follow up was long enough.

Analysis 2.8. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 8 Ovarian cyst formation.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 8 Ovarian cyst formation

Study or subgroup	Progestogen n/N	Placebo/ no Rx n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Prog + Ag vs Ag					
Aston 1995 (1)	5/77	16/75		34.9 %	0.29 [0.12, 0.73]
Ditkoff 1996 (2)	3/47	15/58		28.5 %	0.26 [0.09, 0.71]
Engmann 1999 (3)	3/63	21/54		36.6 %	0.13 [0.05, 0.31]
Subtotal (95% CI)	**187**	**187**		**100.0 %**	**0.21 [0.12, 0.35]**
Total events: 11 (Progestogen), 52 (Placebo/ no Rx)					
Heterogeneity: Chi^2 = 1.89, df = 2 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 5.71 (P < 0.00001)					

(1) Measured after 12 days of pituitary suppression.

(2) Measured after 8 days of pituitary suppression.

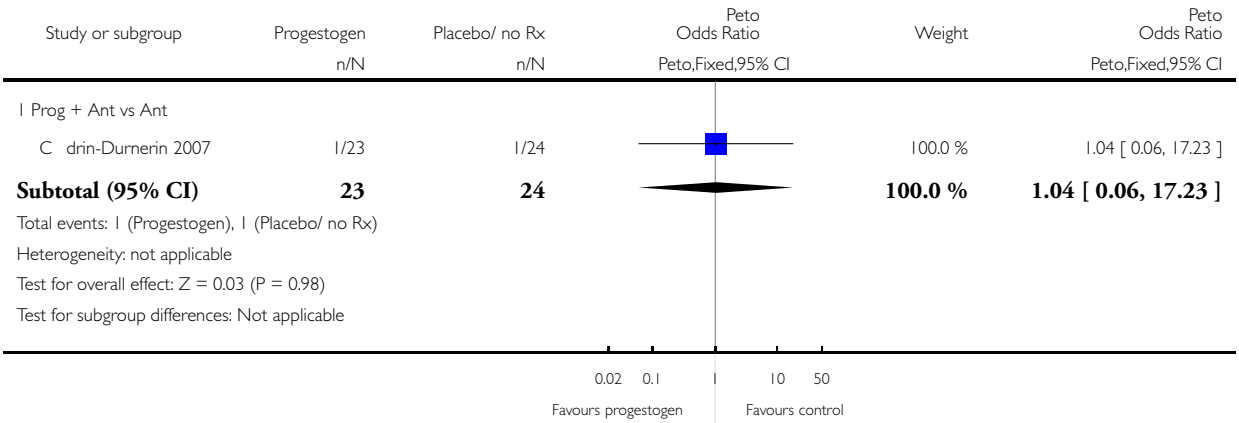
(3) Measured after 7 days of pituitary suppression.

Analysis 2.9. Comparison 2 Progestogen versus placebo/ no Rx, Outcome 9 Multiple pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 2 Progestogen versus placebo/ no Rx

Outcome: 9 Multiple pregnancies

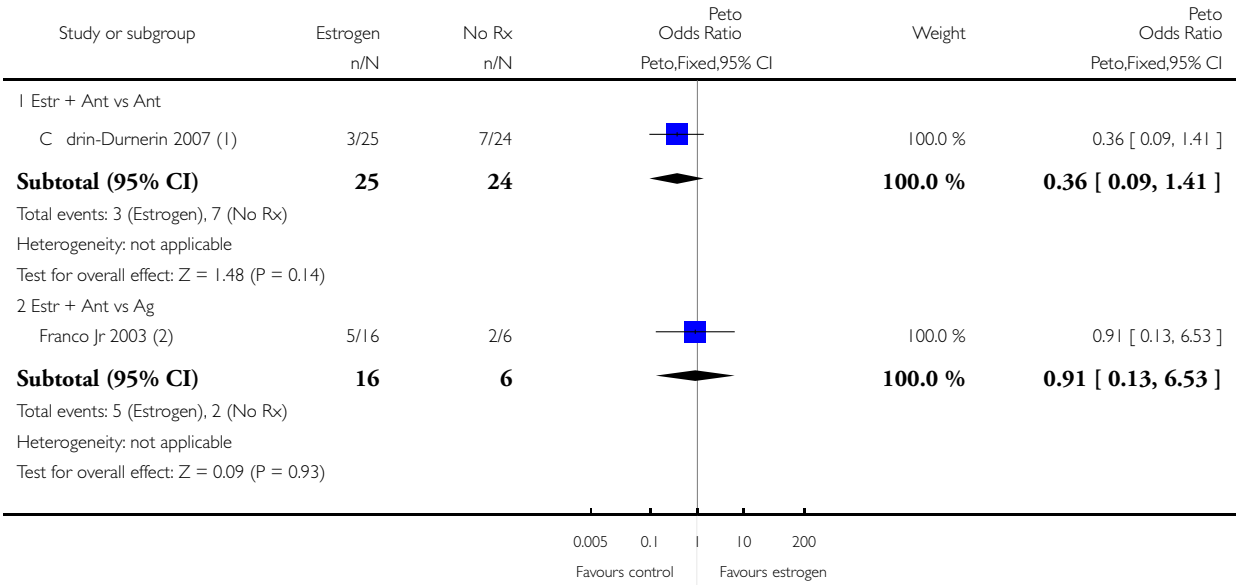


Analysis 3.1. Comparison 3 Estrogen versus no Rx, Outcome 1 Live births.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 1 Live births



(1) Data obtained from Dr. Griesinger.

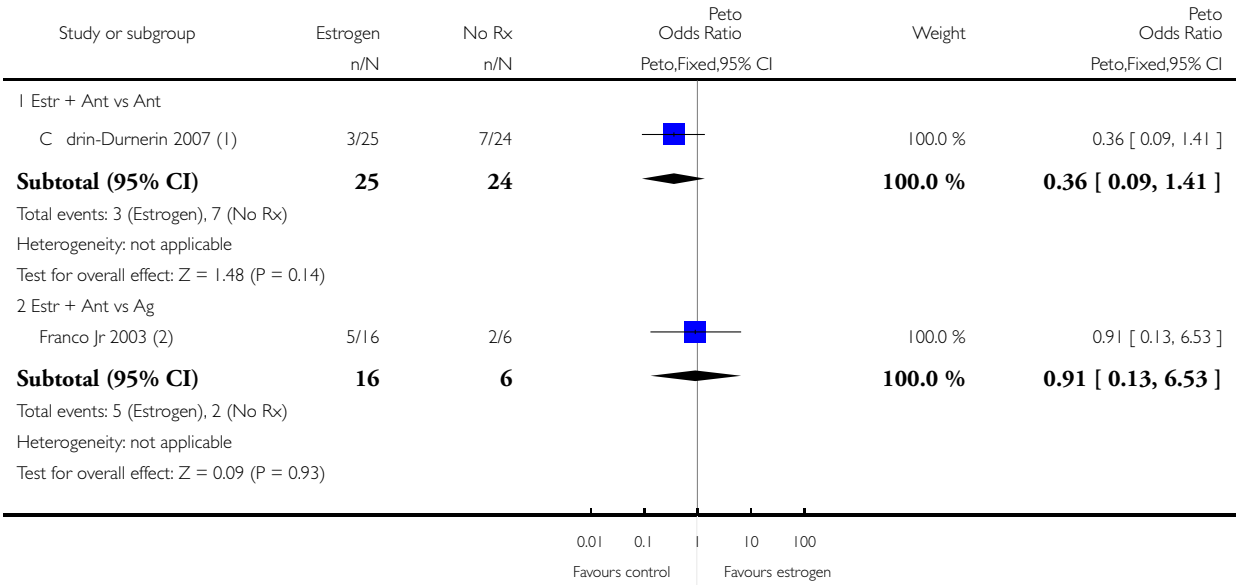
(2) Includes 2 spontaneous pregnancies in the study group. Data obtained from Dr. Franco Jr.

Analysis 3.2. Comparison 3 Estrogen versus no Rx, Outcome 2 Ongoing pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 2 Ongoing pregnancies



(1) Data obtained from Dr. C drin-Durnerin.

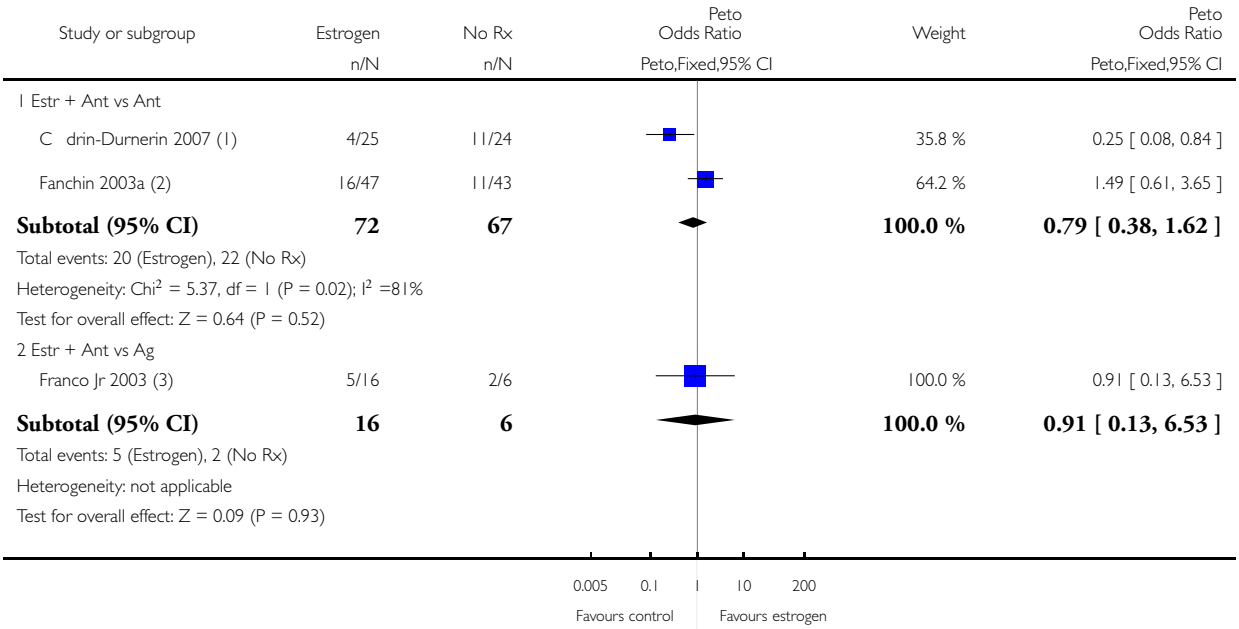
(2) Includes 2 spontaneous pregnancies in the study group.

Analysis 3.3. Comparison 3 Estrogen versus no Rx, Outcome 3 Clinical pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 3 Clinical pregnancies



(1) Data obtained from Dr. C drin-Durnerin.

(2) No ITT. Calculated from rates.

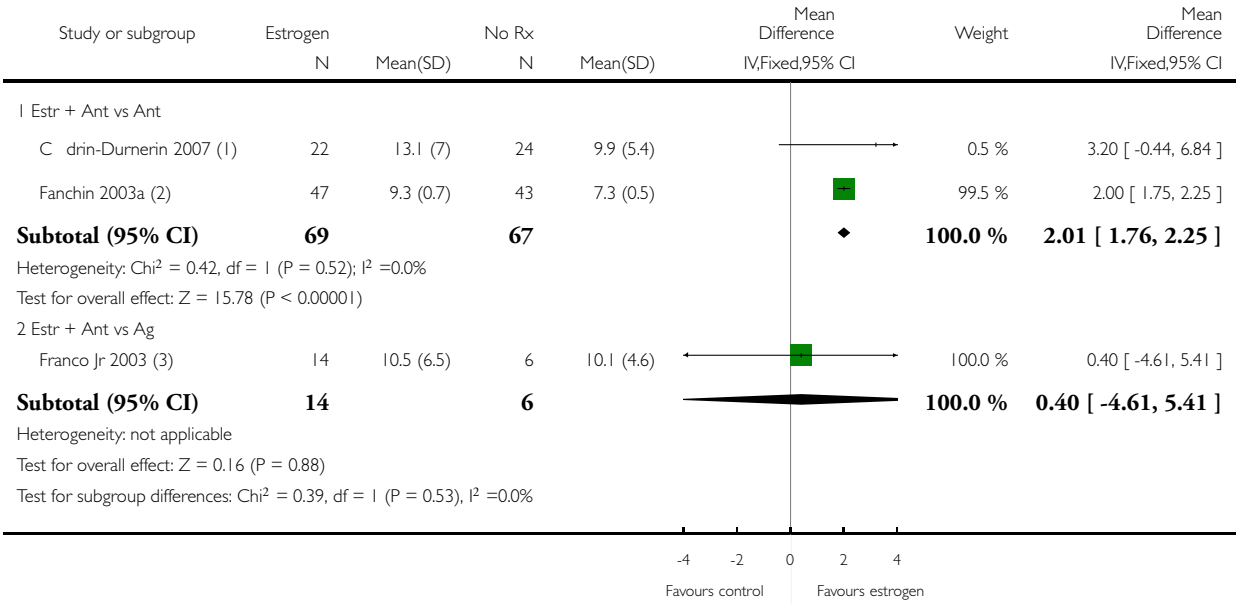
(3) Includes 2 spontaneous pregnancies in the study group.

Analysis 3.4. Comparison 3 Estrogen versus no Rx, Outcome 4 Oocytes retrieved.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 4 Oocytes retrieved



(1) No ITT in estrogen group.

(2) No ITT. 'Mature follicles'.

(3) No ITT.

Analysis 3.5. Comparison 3 Estrogen versus no Rx, Outcome 5 Days of gonadotrophin treatment.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 5 Days of gonadotrophin treatment

Study or subgroup	Estrogen N	Mean(SD)	No Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Estr + Ant vs Ag							
Franco Jr 2003 (1)	14	10.3 (1.6)	6	12.8 (1.7)		100.0 %	-2.50 [-4.10, -0.90]
Subtotal (95% CI)	**14**		**6**			**100.0 %**	**-2.50 [-4.10, -0.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.07 (P = 0.0022)							

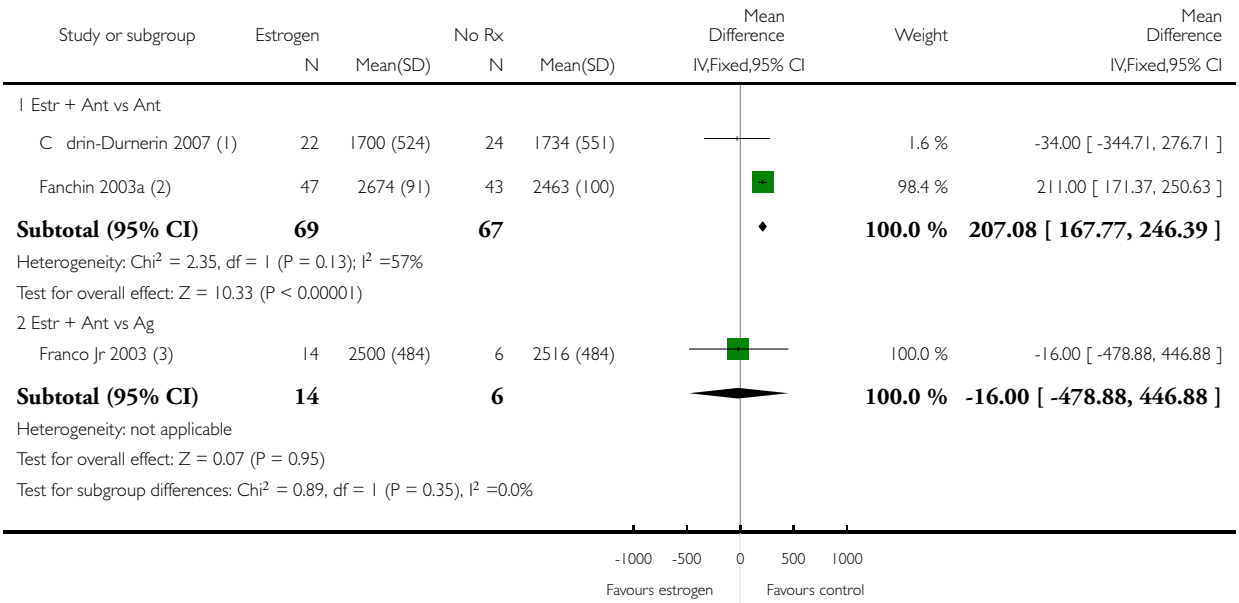
(1) No ITT. Data obtained from Dr. Franco Jr.

Analysis 3.6. Comparison 3 Estrogen versus no Rx, Outcome 6 Amount of gonadotrophins administered.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 6 Amount of gonadotrophins administered



(1) No ITT in estrogen group.

(2) No ITT.

(3) No ITT.

Analysis 3.7. Comparison 3 Estrogen versus no Rx, Outcome 7 Pregnancy losses.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 7 Pregnancy losses

Study or subgroup	Estrogen n/N	No Rx n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Estr + Ant vs Ant				
C drin-Durnerin 2007 (1)	1/25	5/24		0.22 [0.04, 1.17]
Subtotal (95% CI)	**25**	**24**		**0.22 [0.04, 1.17]**
Total events: 1 (Estrogen), 5 (No Rx)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.78 (P = 0.075)				
2 Estr + Ant vs Ag				
Franco Jr 2003	0/16	0/6		0.0 [0.0, 0.0]
Subtotal (95% CI)	**16**	**6**		**0.0 [0.0, 0.0]**
Total events: 0 (Estrogen), 0 (No Rx)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

(1) Calculated from the number of clinical pregnancies minus the number of live births.

Analysis 3.8. Comparison 3 Estrogen versus no Rx, Outcome 8 Ovarian cyst formation.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 8 Ovarian cyst formation

Study or subgroup	Estrogen n/N	No Rx n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Estr + Ant vs Ag				
Franco Jr 2003 (1)	0/16	0/6		0.0 [0.0, 0.0]
Subtotal (95% CI)	**16**	**6**		**0.0 [0.0, 0.0]**
Total events: 0 (Estrogen), 0 (No Rx)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

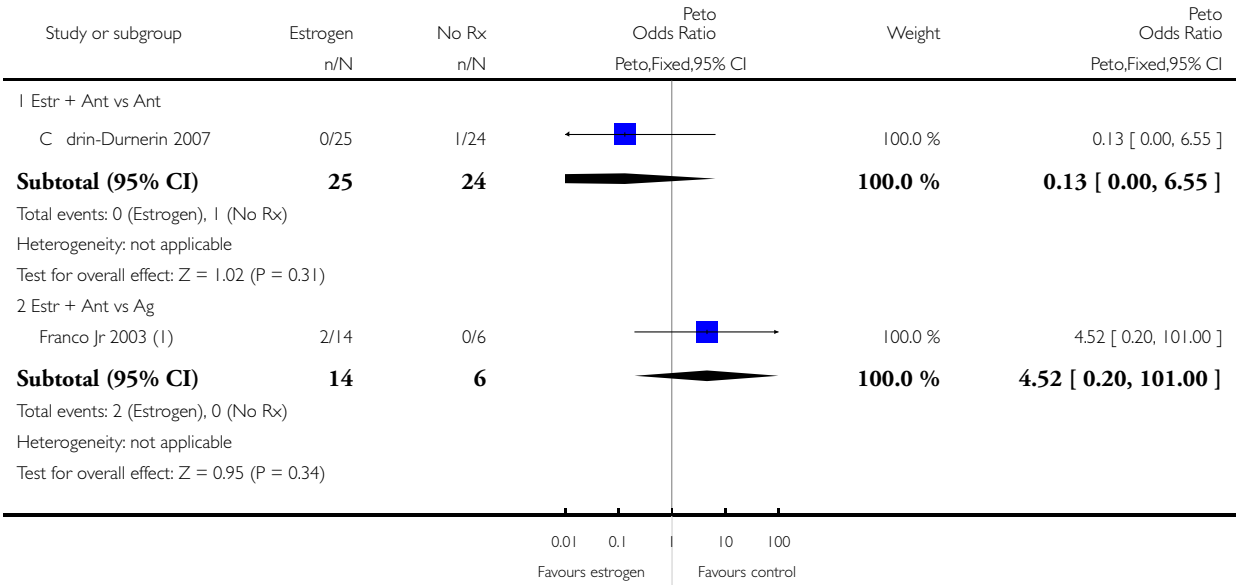
(1) Data obtained from Dr. Franco Jr.

Analysis 3.9. Comparison 3 Estrogen versus no Rx, Outcome 9 Multiple pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 9 Multiple pregnancies



(1) No ITT. Data obtained from Dr. Franco Jr.

Analysis 3.10. Comparison 3 Estrogen versus no Rx, Outcome 10 OHS syndrome.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 3 Estrogen versus no Rx

Outcome: 10 OHS syndrome

Study or subgroup	Estrogen n/N	No Rx n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Estr + Ant vs Ag				
Franco Jr 2003 (1)	0/16	0/6		0.0 [0.0, 0.0]
Subtotal (95% CI)	**16**	**6**		**0.0 [0.0, 0.0]**
Total events: 0 (Estrogen), 0 (No Rx)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

(1) Data obtained from Dr. Franco Jr.

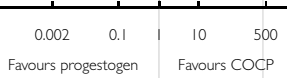
Analysis 4.1. Comparison 4 Combined OCP versus progestogen, Outcome 1 Live births.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 4 Combined OCP versus progestogen

Outcome: 1 Live births

Study or subgroup	Combined OCP n/N	Progestogen n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 COCP + Ant vs Prog + Ant					
C drin-Durnerin 2007	3/21	5/23		100.0 %	0.61 [0.13, 2.79]
Subtotal (95% CI)	**21**	**23**		**100.0 %**	**0.61 [0.13, 2.79]**
Total events: 3 (Combined OCP), 5 (Progestogen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					



Analysis 4.2. Comparison 4 Combined OCP versus progestogen, Outcome 2 Ongoing pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 4 Combined OCP versus progestogen

Outcome: 2 Ongoing pregnancies

Study or subgroup	Combined OCP n/N	Progestogen n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 COCP + Ant vs Prog + Ant					
C drin-Durnerin 2007 (1)	3/21	5/23		100.0 %	0.61 [0.13, 2.79]
Subtotal (95% CI)	**21**	**23**		**100.0 %**	**0.61 [0.13, 2.79]**
Total events: 3 (Combined OCP), 5 (Progestogen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					

(1) Data obtained from Dr. C drin-Durnerin.

Analysis 4.3. Comparison 4 Combined OCP versus progestogen, Outcome 3 Clinical pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 4 Combined OCP versus progestogen

Outcome: 3 Clinical pregnancies

Study or subgroup	Combined OCP n/N	Progestogen n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 COCP + Ant vs Prog + Ant					
C drin-Durnerin 2007 (1)	5/21	7/23		100.0 %	0.72 [0.19, 2.68]
Subtotal (95% CI)	**21**	**23**		**100.0 %**	**0.72 [0.19, 2.68]**
Total events: 5 (Combined OCP), 7 (Progestogen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.49 (P = 0.63)					

(1) Data obtained from Dr. C drin-Durnerin.

Analysis 4.4. Comparison 4 Combined OCP versus progestogen, Outcome 4 Oocytes retrieved.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 4 Combined OCP versus progestogen

Outcome: 4 Oocytes retrieved

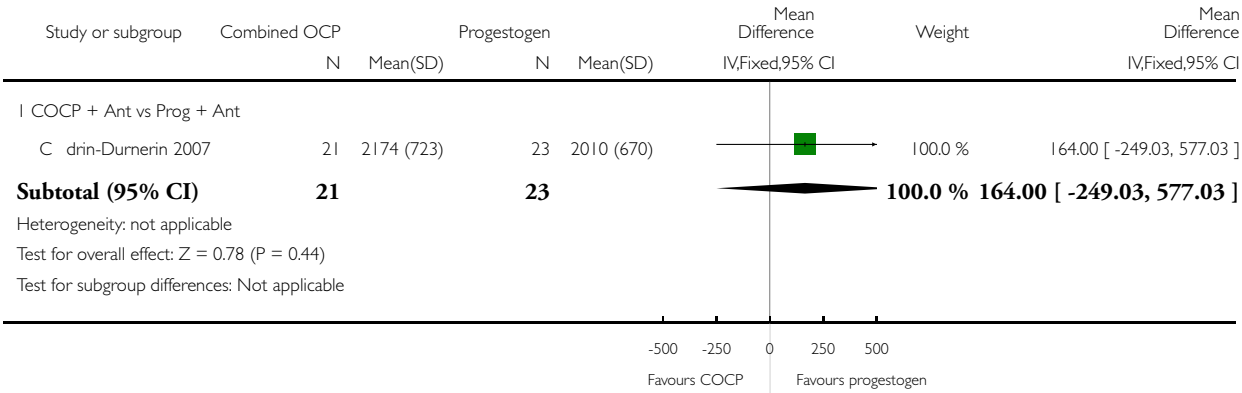
Study or subgroup	Combined OCP N	Mean(SD)	Progestogen N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 COCP + Ant vs Prog + Ant							
C drin-Durnerin 2007	21	14 (8.3)	23	12.6 (7.3)		100.0 %	1.40 [-3.24, 6.04]
Subtotal (95% CI)	**21**		**23**			**100.0 %**	**1.40 [-3.24, 6.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.59 (P = 0.55)							
Test for subgroup differences: Not applicable							

Analysis 4.5. Comparison 4 Combined OCP versus progestogen, Outcome 5 Amount of gonadotrophins administered.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 4 Combined OCP versus progestogen

Outcome: 5 Amount of gonadotrophins administered

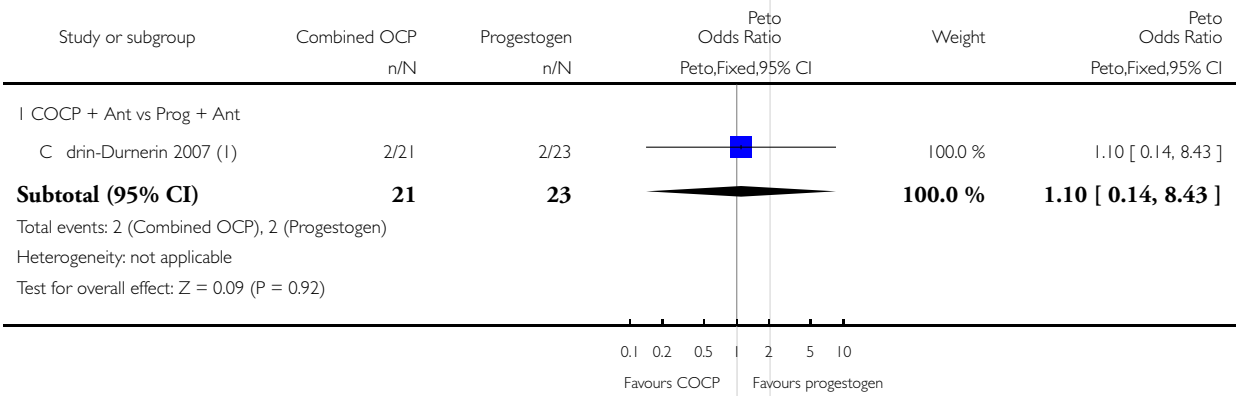


Analysis 4.6. Comparison 4 Combined OCP versus progestogen, Outcome 6 Pregnancy losses.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 4 Combined OCP versus progestogen

Outcome: 6 Pregnancy losses



(1) Calculated from the number of clinical pregnancies minus the number of live births.

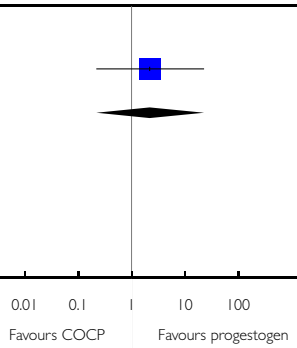
Analysis 4.7. Comparison 4 Combined OCP versus progestogen, Outcome 7 Multiple pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 4 Combined OCP versus progestogen

Outcome: 7 Multiple pregnancies

Study or subgroup	Combined OCP n/N	Progestogen n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 COCP + Ant vs Prog + Ant					
C drin-Durnerin 2007	2/21	1/23		100.0 %	2.22 [0.22, 22.56]
Subtotal (95% CI)	**21**	**23**		**100.0 %**	**2.22 [0.22, 22.56]**
Total events: 2 (Combined OCP), 1 (Progestogen)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
Test for subgroup differences: Not applicable					

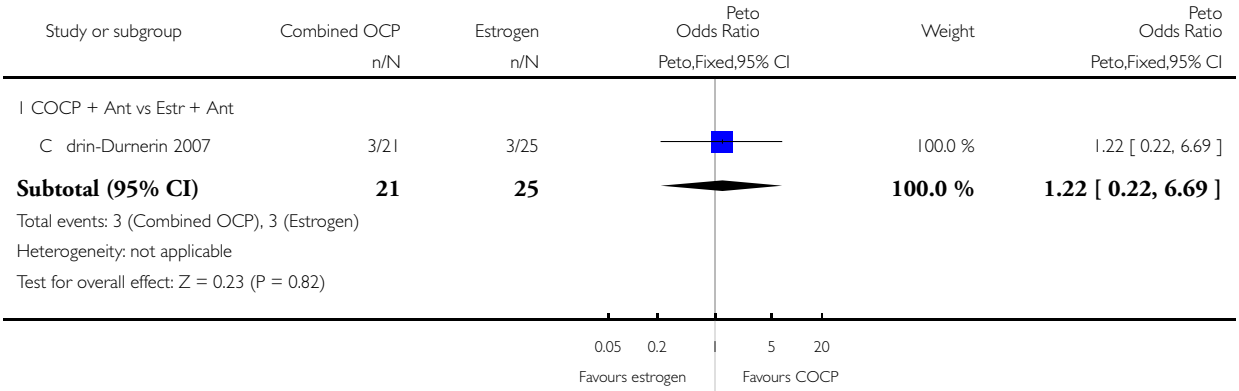


Analysis 5.1. Comparison 5 Combined OCP versus estrogen, Outcome 1 Live births.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 5 Combined OCP versus estrogen

Outcome: 1 Live births

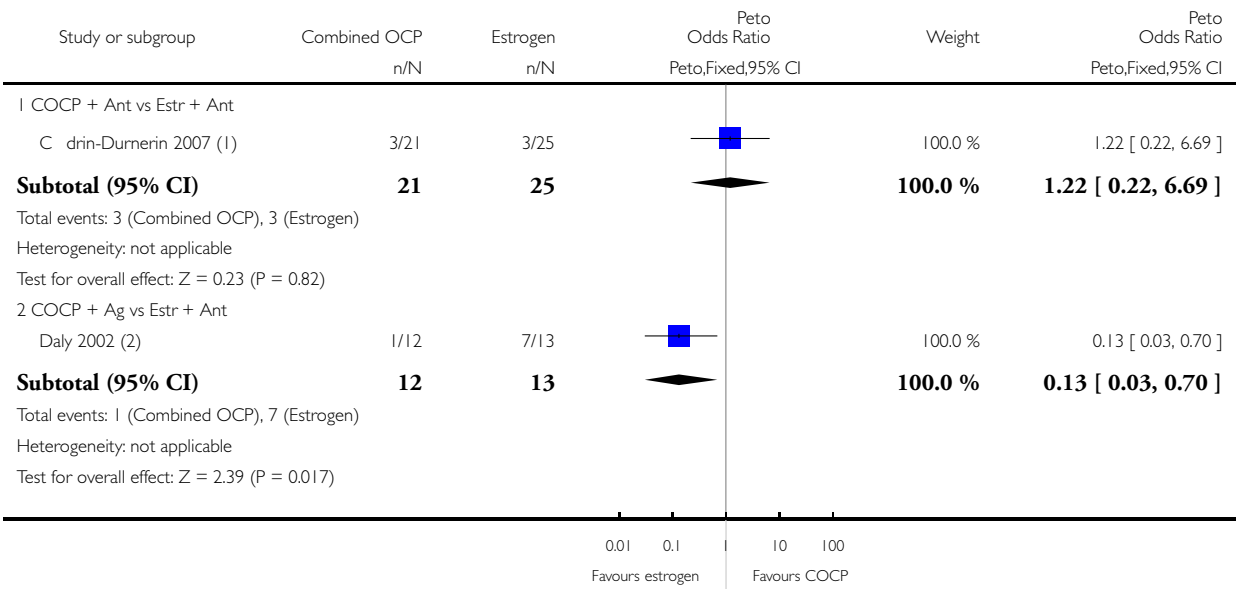


Analysis 5.2. Comparison 5 Combined OCP versus estrogen, Outcome 2 Ongoing pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 5 Combined OCP versus estrogen

Outcome: 2 Ongoing pregnancies



(1) Data obtained from Dr. C drin-Durnerin.

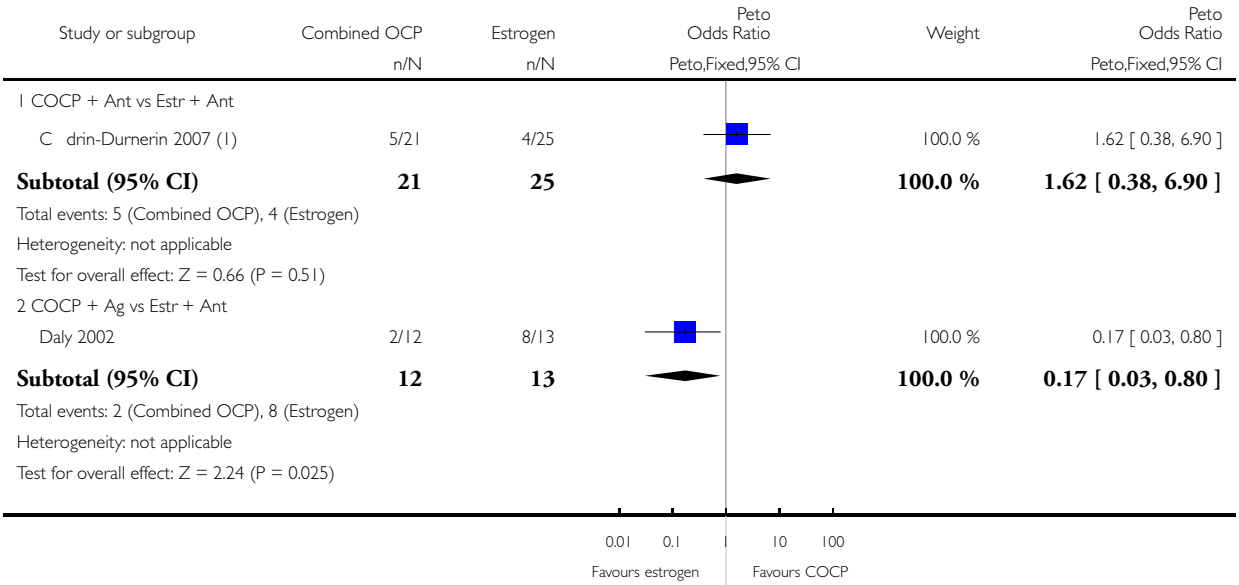
(2) Viable pregnancies

Analysis 5.3. Comparison 5 Combined OCP versus estrogen, Outcome 3 Clinical pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 5 Combined OCP versus estrogen

Outcome: 3 Clinical pregnancies



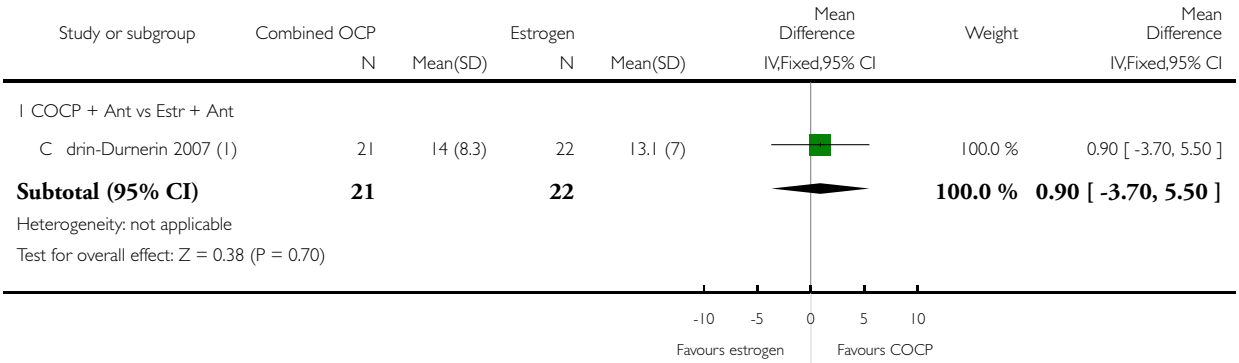
(1) Data obtained from Dr. C drin-Durnerin.

Analysis 5.4. Comparison 5 Combined OCP versus estrogen, Outcome 4 Oocytes retrieved.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 5 Combined OCP versus estrogen

Outcome: 4 Oocytes retrieved



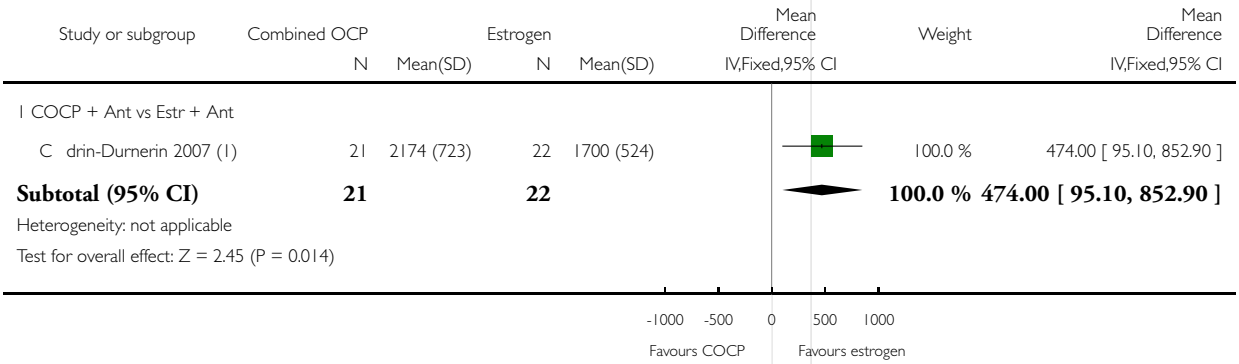
(1) No ITT in estrogen group.

Analysis 5.5. Comparison 5 Combined OCP versus estrogen, Outcome 5 Amount of gonadotrophins administered.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 5 Combined OCP versus estrogen

Outcome: 5 Amount of gonadotrophins administered



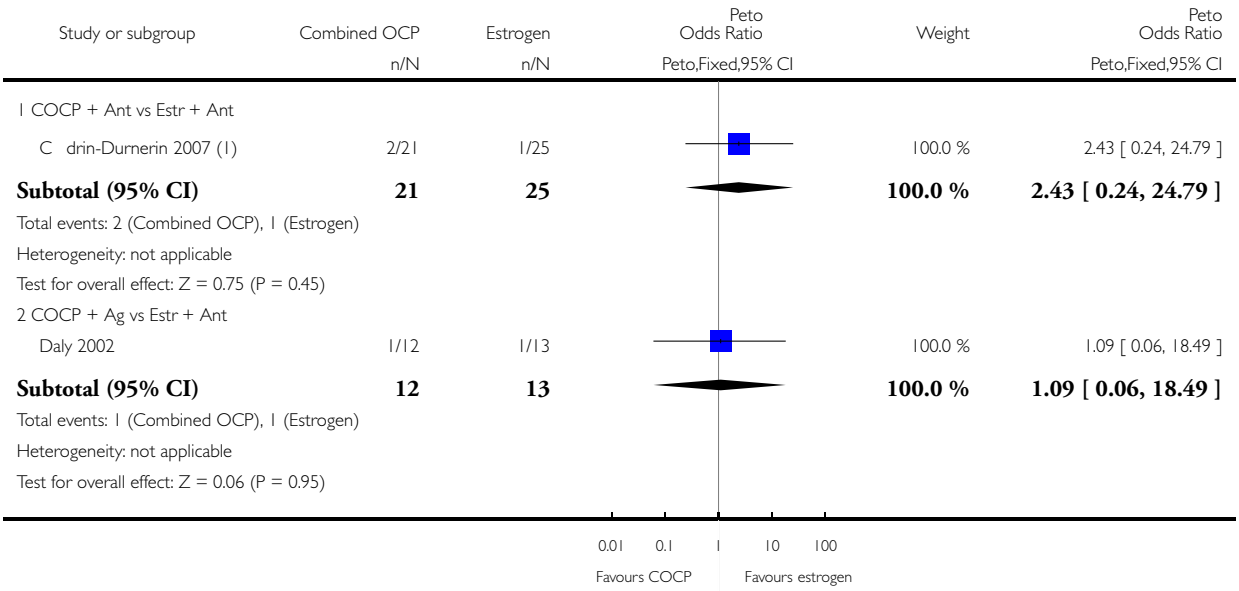
(1) No ITT in estrogen group

Analysis 5.6. Comparison 5 Combined OCP versus estrogen, Outcome 6 Pregnancy losses.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 5 Combined OCP versus estrogen

Outcome: 6 Pregnancy losses



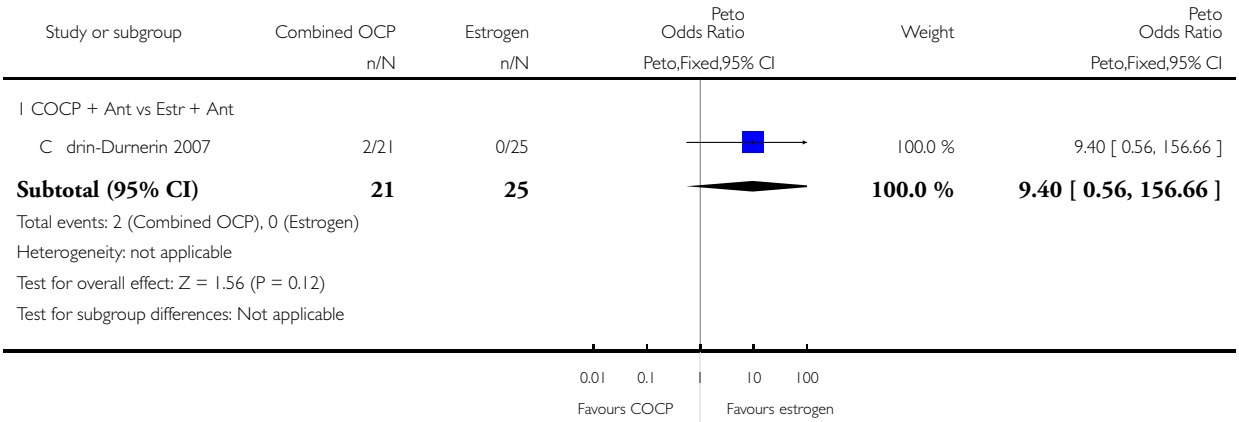
(1) Calculated from the number of clinical pregnancies minus the number of live births.

Analysis 5.7. Comparison 5 Combined OCP versus estrogen, Outcome 7 Multiple pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 5 Combined OCP versus estrogen

Outcome: 7 Multiple pregnancies

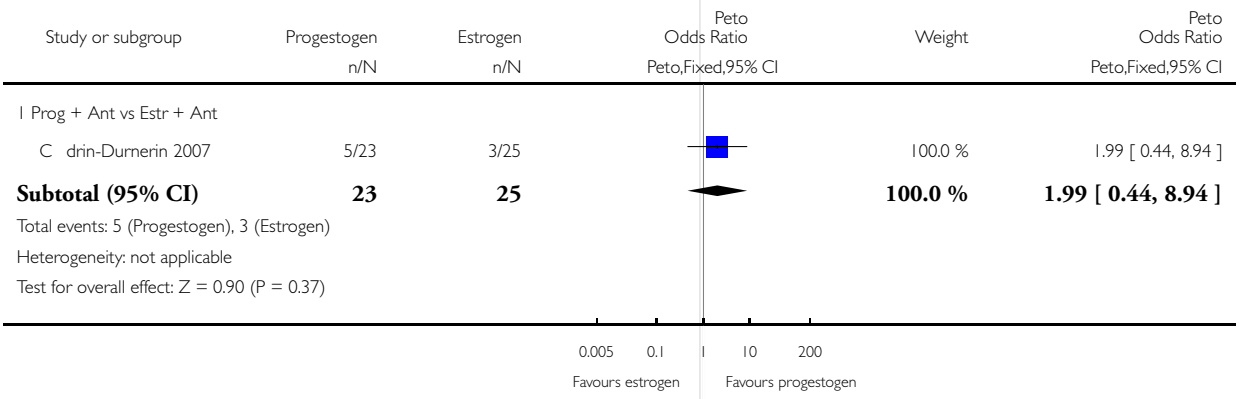


Analysis 6.1. Comparison 6 Progestogen versus estrogen, Outcome 1 Live births.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 6 Progestogen versus estrogen

Outcome: 1 Live births

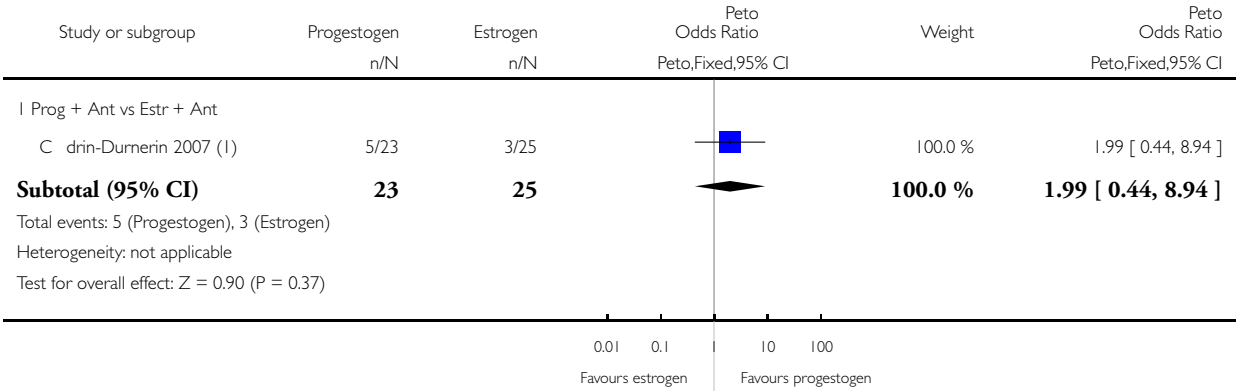


Analysis 6.2. Comparison 6 Progestogen versus estrogen, Outcome 2 Ongoing pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 6 Progestogen versus estrogen

Outcome: 2 Ongoing pregnancies



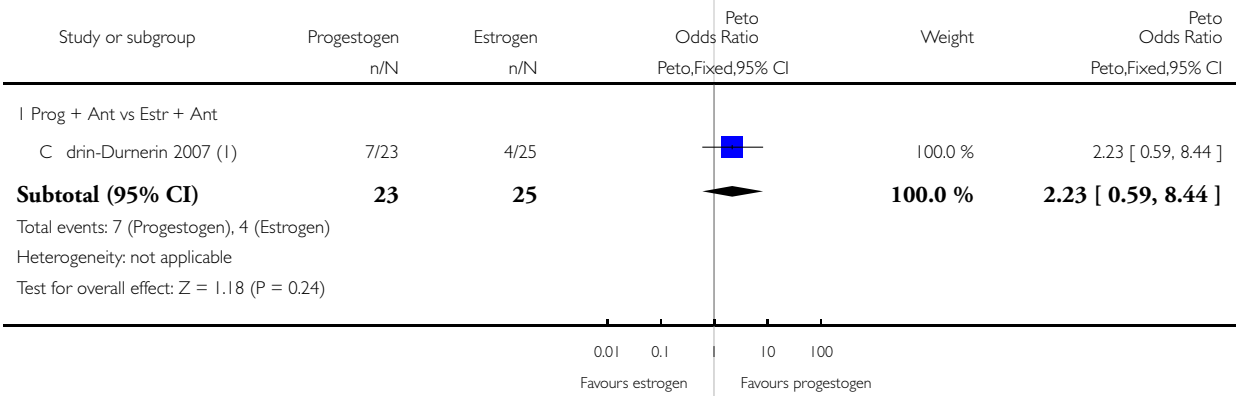
(1) Data obtained from Dr. C drin-Durnerin.

Analysis 6.3. Comparison 6 Progestogen versus estrogen, Outcome 3 Clinical pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 6 Progestogen versus estrogen

Outcome: 3 Clinical pregnancies



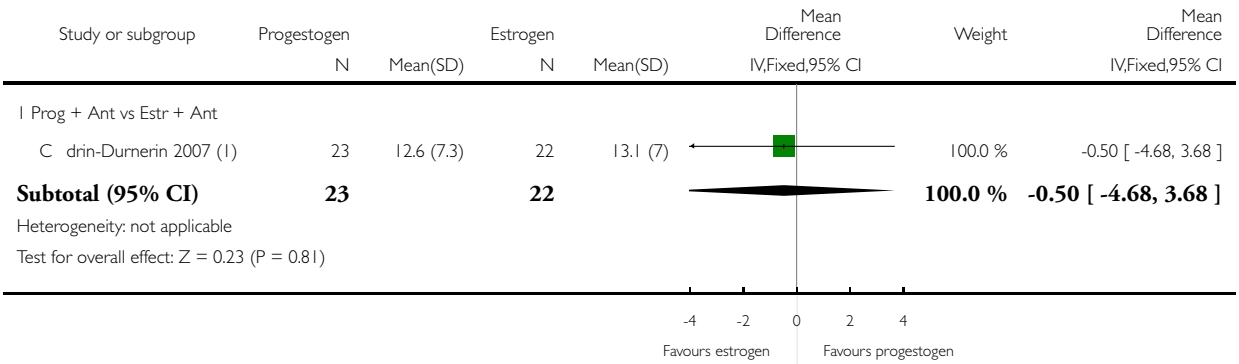
(1) Data obtained from Dr. C drin-Durnerin.

Analysis 6.4. Comparison 6 Progestogen versus estrogen, Outcome 4 Oocytes retrieved.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 6 Progestogen versus estrogen

Outcome: 4 Oocytes retrieved



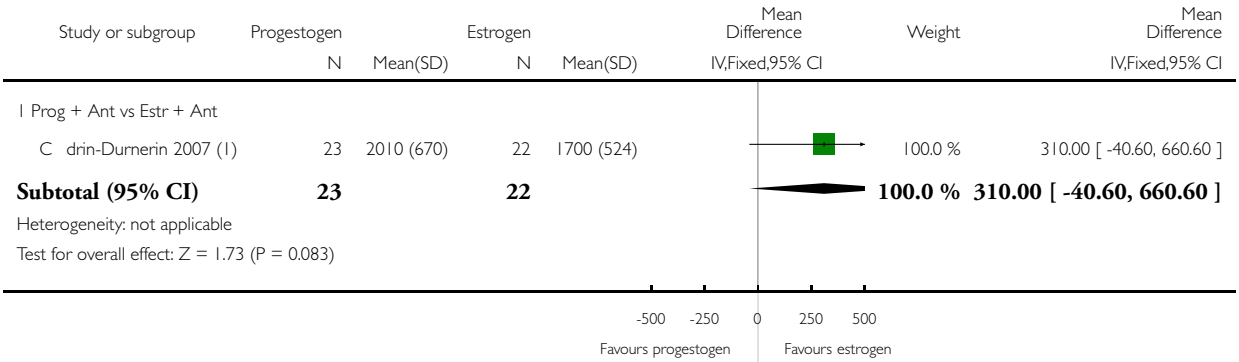
(1) No ITT in estrogen group.

Analysis 6.5. Comparison 6 Progestogen versus estrogen, Outcome 5 Amount of gonadotrophins administered.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 6 Progestogen versus estrogen

Outcome: 5 Amount of gonadotrophins administered



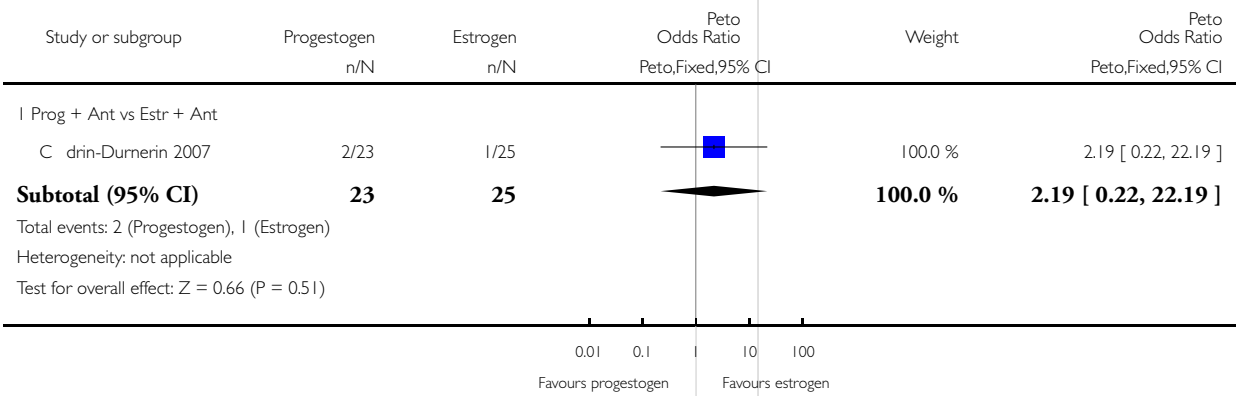
(1) No ITT in estrogen group.

Analysis 6.6. Comparison 6 Progestogen versus estrogen, Outcome 6 Pregnancy losses.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 6 Progestogen versus estrogen

Outcome: 6 Pregnancy losses

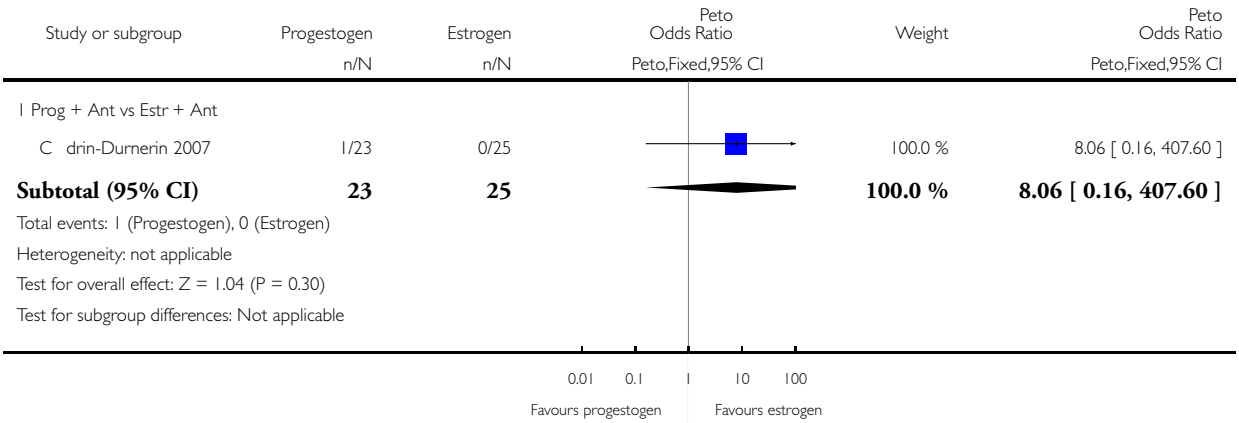


Analysis 6.7. Comparison 6 Progestogen versus estrogen, Outcome 7 Multiple pregnancies.

Review: Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques

Comparison: 6 Progestogen versus estrogen

Outcome: 7 Multiple pregnancies



ADDITIONAL TABLES

Table 1. Heterogeneity Analysis 1.4.2 + 1.5.2 + 1.6.2

	Cédrin-Durnerin 2007	Huirne 2006b	Kolibianakis 2006	Obruca 2001	Rombauts 2006
Inclusion criteria					
Age limit used	< 38	< 38	< 39	No limit	< 39
Only regular cycles	Yes	Yes	No	No	Yes
Exclusion criteria					
Poor responders included	Yes	No	Yes	No	Yes
Pre-treatment					
Type of OCP	Ethinyl estradiol + Desogestrel	Ethinyl estradiol + Levonorgestrel	Ethinyl estradiol + Desogestrel	Ethinyl estradiol + Desogestrel	Ethinyl estradiol + Desogestrel
Starting day	CD 2 or 3	CD 2 or 3	CD 1	CD 1	CD 1

Table 1. Heterogeneity Analysis 1.4.2 + 1.5.2 + 1.6.2 (*Continued*)

Duration	15-21 days	14-28 days	14 days	18-28 days	14-28 days
GnRH analogue					
Type antagonist	Ganirelix	Antide	Ganirelix	Cetrorelix	Ganirelix
Dose	0.25 mg/day	0.5 mg/mL	Unknown	0.25 mg/day	0.25 mg/day
Starting day	Follicle > 14 mm	SD 6	Unknown	SD 6	CD 21-24
Gonadotrophins					
Type	rFSH	rFSH	rFSH	rFSH	rFSH
Dose (IU/day)	150-300	150-300	200	150	200

CD = Cycle Day
SD = Stimulation Day

Table 2. Heterogeneity Analysis 1.5.3 + 1.6.3.

	Huirne 2006a	Hwang 2004	Rombauts 2006
Inclusion criteria			
Only PCOS included	No	Yes	No
Pre-treatment			
Type of OCP	Ethinyl estradiol + Levonorgestrel	Ethinyl estradiol + Cyproterone acetate	Ethinyl estradiol + Desogestrel
Starting day	CD 1 to 5	CD 5	CD 1
Duration	21 to 28 days	three cycles	14 to 28 days
GnRH analogue			
Type antagonist	Cetrorelix	Cetrorelix	Ganirelix
Dose (mg/day)	0.25	0.25	0.25
Starting day	SD 6	PD 3	SD 5 or 6
Type agonist	Buserelin	Buserelin	Nafarelin

Table 2. Heterogeneity Analysis 1.5.3 + 1.6.3. (*Continued*)

Dose (μg/day)	500	500	800
Starting day	CD 18 to 22	CD 3	CD 21 to 24
Gonadotrophins			
Type	rFSH	hMG	rFSH
Dose (IU/day)	150 to 225	150	200

CD = Cycle Day
SD = Stimulation Day
PD = Post-treatment Day

Table 3. Heterogeneity Analysis 3.6.1

	Cédrin-Durnerin 2007	Fanchin 2003a
Inclusion criteria		
Age limit	< 38	< 39
Pre-treatment		
Type of oestrogen	Micronized 17-βE_2	Micronized 17-βE_2
Starting day	10 days before presumed menses	CD 20
Duration	10 to 15 days	11 days
GnRH analogue		
Type antagonist	Ganirelix	Cetrorelix
Dose	0.25 mg/day	3 mg (single dose)
Starting day	Follicle > 14 mm	$\geq$ 1 follicle < 13 mm in diameter
Gonadotrophins		
Type	rFSH	rFSH
Dose (IU/day)	150 to 300	225

APPENDICES

Appendix 1. MDSG Specialised Register search strategy

Keywords CONTAINS 'IVF' or 'in vitro fertilization' or 'in-vitro fertilisation' or 'in-vitro fertilization' or 'ICSI' or 'intracytoplasmic sperm injection' or 'embryo' or 'ART' or 'controlled ovarian' or ' COH' or Title CONTAINS 'IVF' or 'in vitro fertilization' or 'in-vitro fertilisation' or 'in-vitro fertilization' or 'ICSI' or 'intracytoplasmic sperm injection' or 'embryo' or 'ART' or 'controlled ovarian' or ' COH'
AND
Keywords CONTAINS 'oral contraceptive' or 'oral contraceptives' or 'OCP' or 'oral contraceptive agent' or 'combined oral contraceptives' or 'progestagen' or 'progesterone' or 'progestin' or 'progestogen' or 'norgestrel' or 'norethisterone' or 'desogestrel' or 'gestodene' or 'oestrogen' or 'oestrogen' or 'oestrodiol' or 'estradiol' or 'pretreatment' or Title CONTAINS 'oral contraceptive' or 'oral contraceptives' or 'oral contraceptive agent' or 'combined oral contraceptives' or 'progestagen' or 'progesterone' or 'progestin' or 'progestogen' or 'norgestrel' or 'norethisterone' or 'desogestrel' or 'gestodene' or 'oestrogen' or 'oestrogen' or 'oestrodiol' or 'estradiol' or 'pretreatment'

Appendix 2. CENTRAL search strategy

1 reproductive techniques/ or exp reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp gamete intrafallopian transfer/
2 ART.tw.
3 (IVF or ICSI).tw.
4 embryo transfer.tw.
5 (in vitro fertilisation or in vitro fertilization).tw.
6 intracytoplasmic sperm injection$.tw.
7 COH.tw.
8 ovar$ stimulat$.tw.
9 or/1-8
10 oral contracepti$.tw.
11 (OC or OCP$).tw.
12 (pretreatment$ or pre-treatment$).tw.
13 contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp desogestrel/ or exp dimethisterone/ or exp levonorgestrel/ or exp norethindrone/ or exp norgestrel/ or exp norgestrienone/
14 gestrinone$.tw.
15 ethinyl estradiol.tw.
16 norgestrel.tw.
17 desogestrel.tw.
18 dimethisterone.tw.
19 levonorgestrel.tw.
20 norethindrone.tw.
21 norgestrel.tw.
22 norgestrienone.tw.
23 gestodene.tw.
24 norgestimate.tw.
25 dienogest.tw.
26 progestogen$.tw.
27 progestagen$.tw.
28 progestin$.tw.
29 or/10-27
30 9 and 29
31 luteal phase.ti.
32 luteal support.ti.
33 or/31-32

34 30 not 33

Appendix 3. MEDLINE search strategy

1 reproductive techniques/ or exp reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp gamete intrafallopian transfer/
2 ART.tw.
3 (IVF or ICSI).tw.
4 embryo transfer.tw.
5 (in vitro fertilisation or in vitro fertilization).tw.
6 intracytoplasmic sperm injection$.tw.
7 COH.tw.
8 ovar$ stimulat$.tw.
9 or/1-8
10 oral contracepti$.tw.
11 (OC or OCP$).tw.
12 (pretreatment$ or pre-treatment$).tw.
13 contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp desogestrel/ or exp dimethisterone/ or exp levonorgestrel/ or exp norethindrone/ or exp norgestrel/ or exp norgestrienone/
14 gestrinone$.tw.
15 ethinyl estradiol.tw.
16 norgestrel.tw.
17 desogestrel.tw.
18 dimethisterone.tw.
19 levonorgestrel.tw.
20 norethindrone.tw.
21 norgestrel.tw.
22 norgestrienone.tw.
23 gestodene.tw.
24 norgestimate.tw.
25 dienogest.tw.
26 progestogen$.tw.
27 progestagen$.tw.
28 progestin$.tw.
29 or/10-27
30 9 and 29
31 randomised controlled trial.pt.
32 controlled clinical trial.pt.
33 (randomised or randomised).ab.
34 placebo.ab.
35 drug therapy.fs.
36 randomly.ab.
37 trial.ab.
38 groups.ab.
39 or/31-38
40 (animals not (humans and animals)).sh.
41 39 not 40
42 41 and 30
43 luteal support.ti.
44 luteal phase.ti.
45 43 or 44

46 42 not 45

Appendix 4. EMBASE search strategy

1 reproductive techniques/ or exp reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp gamete intrafallopian transfer/
2 ART.tw.
3 (IVF or ICSI).tw.
4 embryo transfer.tw.
5 (in vitro fertilisation or in vitro fertilization).tw.
6 intracytoplasmic sperm injection$.tw.
7 COH.tw.
8 ovar$ stimulat$.tw.
9 or/1-8
10 oral contracepti$.tw.
11 (OC or OCP$).tw.
12 (pretreatment$ or pre-treatment$).tw.
13 contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp desogestrel/ or exp dimethisterone/ or exp levonorgestrel/ or exp norethindrone/ or exp norgestrel/ or exp norgestrienone/
14 gestrinone$.tw.
15 ethinyl estradiol.tw.
16 norgestrel.tw.
17 desogestrel.tw.
18 dimethisterone.tw.
19 levonorgestrel.tw.
20 norethindrone.tw.
21 norgestrel.tw.
22 norgestrienone.tw.
23 gestodene.tw.
24 norgestimate.tw.
25 dienogest.tw.
26 progestogen$.tw.
27 progestagen$.tw.
28 progestin$.tw.
29 or/10-27
30 9 and 29
31 luteal phase.ti.
32 luteal support.ti.
33 or/31-32
34 30 not 33
35 Clinical Trial/ (520486)
36 Randomized Controlled Trial/
37 exp randomization/
38 Single Blind Procedure/
39 Double Blind Procedure/
40 Crossover Procedure/
41 Placebo/
42 Randomi?ed controlled trial$.tw.
43 Rct.tw.
44 random allocation.tw.
45 randomly allocated.tw.

46 allocated randomly.tw.
47 (allocated adj2 random).tw.
48 Single blind$.tw.
49 Double blind$.tw.
50 ((treble or triple) adj blind$).tw.
51 placebo$.tw.
52 prospective study/
53 or/35-52
54 case study/
55 case report.tw.
56 abstract report/ or letter/
57 or/54-56
58 53 not 57
59 34 and 58
60 limit 59 to yr="2007 - 2008"

Appendix 5. CINAHL search strategy

1 reproductive techniques/ or exp reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp gamete intrafallopian transfer/
2 ART.tw.
3 (IVF or ICSI).tw.
4 embryo transfer.tw.
5 (in vitro fertilisation or in vitro fertilization).tw.
6 intracytoplasmic sperm injection$.tw.
7 COH.tw.
8 ovar$ stimulat$.tw.
9 or/1-8
10 oral contracepti$.tw.
11 (OC or OCP$).tw.
12 (pretreatment$ or pre-treatment$).tw.
13 contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp desogestrel/ or exp dimethisterone/ or exp levonorgestrel/ or exp norethindrone/ or exp norgestrel/ or exp norgestrienone/
14 gestrinone$.tw.
15 ethinyl estradiol.tw.
16 norgestrel.tw.
17 desogestrel.tw.
18 dimethisterone.tw.
19 levonorgestrel.tw.
20 norethindrone.tw.
21 norgestrel.tw.
22 norgestrienone.tw.
23 gestodene.tw.
24 norgestimate.tw.
25 dienogest.tw.
26 progestogen$.tw.
27 progestagen$.tw.
28 progestin$.tw.
29 or/10-27
30 9 and 29
31 luteal phase.ti.

32 luteal support.ti.
33 or/31-32
34 30 not 33
35 exp clinical trials/
36 Clinical trial.pt.
37 (clinic$ adj trial$1).tw.
38 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.
39 Randomi?ed control$ trial$.tw.
40 Random assignment/
41 Random$ allocat$.tw.
42 Placebo$.tw.
43 Placebos/
44 Quantitative studies/
45 Allocat$ random$.tw.
46 or/35-45
47 34 and 46

Appendix 6. PsycINFO search strategy

1 reproductive techniques/ or exp reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or exp gamete intrafallopian transfer/
2 ART.tw.
3 (IVF or ICSI).tw.
4 embryo transfer.tw.
5 (in vitro fertilisation or in vitro fertilization).tw.
6 intracytoplasmic sperm injection$.tw.
7 COH.tw.
8 ovar$ stimulat$.tw.
9 or/1-8
10 oral contracepti$.tw.
11 (OC or OCP$).tw.
12 (pretreatment$ or pre-treatment$).tw.
13 contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp desogestrel/ or exp dimethisterone/ or exp levonorgestrel/ or exp norethindrone/ or exp norgestrel/ or exp norgestrienone/
14 gestrinone$.tw.
15 ethinyl estradiol.tw.
16 norgestrel.tw.
17 desogestrel.tw.
18 dimethisterone.tw.
19 levonorgestrel.tw.
20 norethindrone.tw.
21 norgestrel.tw.
22 norgestrienone.tw.
23 gestodene.tw.
24 norgestimate.tw.
25 dienogest.tw.
26 progestogen$.tw.
27 progestagen$.tw.
28 progestin$.tw.
29 or/10-27
30 9 and 29

31 luteal phase.ti.
32 luteal support.ti.
33 or/31-32
34 30 not 33

Appendix 7. Data extraction form (part 1)

Assessment	
Assessor	SvO / BS
Date	

Final conclusion
Inclusion
Exclusion Reason for exclusion:

A. Study information	
1. Title	
2. First author	
3. Year	
4. Published	Yes / No
5. Journal	

B. Criteria for eligibility		**YES**	**NO**
Design	Described as randomised? *If no, then exclude*		
Patients	Women with subfertility, regardless of any cause, undergoing ART		

(*Continued*)

Intervention	· OCP prior to gonadotrophins · OCP prior to gonadotrophins + GnRH agonist · OCP prior to gonadotrophins + GnRH antagonist · Estrogen prior to gonadotrophins · Estrogen prior to gonadotrophins + GnRH agonist · Estrogen prior to gonadotrophins + GnRH antagonist · Progestogen prior to gonadotrophins · Progestogen prior to gonadotrophins + GnRH agonist · Progestogen prior to gonadotrophins + GnRH antagonist		

B. Criteria for eligibility (continued)		**YES**	**NO**
Comparison	· Placebo prior to gonadotrophins · Placebo prior to gonadotrophins + GnRH agonist · Placebo prior to gonadotrophins + GnRH antagonist · No pretreatment prior to gonadotrophins · No pretreatment prior to gonadotrophins + GnRH agonist · No pretreatment prior to gonadotrophins + GnRH antagonist · OCP prior to gonadotrophins · OCP prior to gonadotrophins + GnRH agonist · OCP prior to gonadotrophins + GnRH antagonist · Estrogen prior to gonadotrophins · Estrogen prior to gonadotrophins + GnRH agonist		

(*Continued*)

	· Estrogen prior to gonadotrophins + GnRH antagonist · Progestogen prior to gonadotrophins · Progestogen prior to gonadotrophins + GnRH agonist · Progestogen prior to gonadotrophins + GnRH antagonist		
Outcome	Primary: · number of live births Secondary: · no. of ongoing pregnancies · no. of clinical pregnancies · no. of oocytes retrieved · total days of gonadotrophin treatment · amount of gonadotrophin administered Adverse: · no. of pregnancy loss · no. of ovarian cyst formation · no. of multiple pregnancies · no. of ovarian hyperstimulation syndrome		
Remarks:			

C. Characteristics			
C1. Trial characteristics			
Country of investigation			
Setting	Single	Multicentre	Unclear
	Academic	Non-academic	Unclear
Duration of trial	Y =	M =	D =
Design	Parallel	Crossover	
Number of participants	Inter-ven-		

(*Continued*)

	tion group Comparison group Total:	
Remarks:		

C2. Participants characteristics

	Intervention group		Comparison group	
Age	Mean: SD: Not reported:		Mean: SD: Not reported:	
BMI	Mean: SD: Not reported:		Mean: SD: Not reported:	
Duration of subfertility	Mean: SD: Not reported:		Mean: SD: Not reported:	
No. of previous IVF trials	Mean: SD: Not reported:		Mean: SD: Not reported:	
Subfertility	Primary: Secondary: Not reported:	N = N =	Primary: Secondary: Not reported:	N = N =
Causes of subfertility	Tubal: Male: Endometriosis: Idiopathic: Other: Not reported:	N = N = N = N = N =	Tubal: Male: Endometriosis: Idiopathic: Other: Not reported:	N = N = N = N = N =
Poor response	YES NO Defined as: * Mature ovarian follicles: < 3 with a mean diameter ≥ 17 mm * Oocytes retrieved:			

(*Continued*)

	< 3 * Other:

C2. Flowchart of participants
Remarks:

C3. Protocol characteristics	
Pre-treatment	Combined OCP Estrogen Progestogen Name of preparation: Dosage: Start: Stop:
Ovarian stimulation	hMG rFSH Name of preparation: Dosage: Start: Stop:
Pituitary desensitization	GnRH agonist GnRH antagonist Name of preparation: Dosage: Start: Stop: Protocol:
Treatment schedule	

C4. Follow-up		
Duration of follow-up		
Analysis of loss to follow-up	Per protocol	Intention-to-treat
Remarks:		

D. Risk of bias assessment				
		YES	NO	Unclear
Study size	Was a power calculation performed and adhered?			

(*Continued*)

Selection bias	Was the allocation sequence adequately generated?			
	Was the patient allocation concealment adequate?			
Detection bias	Was the length of follow-up long enough to detect stated outcomes?			
	Was the investigator (performer of hormone administration) blinded?			
	Was the outcome assessor blinded?			
	Were the participants blinded?			
Attrition bias	Was loss to follow up accounted for?			
	Was an intention-to-treat analysis performed?			
Reporting bias	Where there any suggestions of selective report of outcome?			
Source of funding	Is the source of funding stated?			
Remarks:				

Appendix 8. Data extraction form (part 2)

D. Risk of bias assessment				
		YES	NO	Unclear
Study size	Was a power calculation performed and adhered?			

(*Continued*)

Selection bias	Was the allocation sequence adequately generated?			
	Was the patient allocation concealment adequate?			
Detection bias	Was the length of follow-up long enough to detect stated outcomes?			
	Was the investigator (performer of hormone administration) blinded?			
	Was the outcome assessor blinded?			
	Were the participants blinded?			
Attrition bias	Was loss to follow up accounted for?			
	Was an intention-to-treat analysis performed?			
Reporting bias	Where there any suggestions of selective report of outcome?			
Source of funding	Is the source of funding stated?			
Remarks:				

E. Outcomes	
Comparison	a. Define treatment: b. Define control:

E1. Primary outcomes

Live births		No. of live birth	No. of no live birth	Total
Defined: YES NO	Treatment group			
	Control group			
	Total			

Remarks:

E2. Secondary outcomes

Ongoing pregnancy		No. of ongoing pregnancy	No. of no ongoing pregnancy	Total
Defined: YES NO	Treatment group			
	Control group			
	Total			

Remarks:

Clinical pregnancy		No. of clinical pregnancy	No. of no clinical pregnancy	Total
Defined: YES NO	Treatment group			
	Control group			
	Total			
Remarks:				

Oocytes retrieved		Mean no. of oocytes retrieved	SD
Defined: YES NO	Treatment group		
	Control group		
Remarks:			

Days of gonadotrophins treatment		Mean no. of days of gonadotrophins treatment	SD
Defined: YES NO	Treatment group		
	Con-		

(*Continued*)

	trol grou		

Remarks:

Total days of treatment Defined: YES NO		Mean no. of days of pituitary suppression	SD
	Treatment grou		
	Control grou		

Remarks:

E3. Adverse outcomes

Pregnancy loss Defined: YES NO		No. of pregnancy loss	No. of no pregnancy loss	Total
	Treatment group			
	Control group			
	Total			

Remarks:

Ovarian cyst formation Defined: YES NO		No. of ovarian cyst formation	No. of no ovarian cyst formation	Total
	Treatment group			
	Control group			

(*Continued*)

	Total			
Remarks:				

Multiple pregnancy Defined: YES NO		No. of multiple pregnancies	No. of no multiple pregnancies	Total
	Treatment group			
	Control group			
	Total			
Remarks:				

Ovarian hyperstimulation syndrome Defined: YES NO		No. of OHS syndrome	No. of no OHS syndrome	Total
	Treatment group			
	Control group			
	Total			
Remarks:				

Appendix 9. Glossary

Embryo The product of conception from the time of fertilisation to the end of the embryonic stage eight weeks after fertilisation.
Embryo transfer (ET) Procedure of which embryos are placed in the uterus or fallopian tube.
Endogenous Developed or originated inside the organism. For example hormones produced by the pituitary gland would be an endogenous supply, but hormones produced in the laboratory and then given to the body is called an **exogenous** supply.
Fertilisation The penetration of the ovum by the sperm cell and fusion of genetic materials, resulting in the development of an embryo.
Follicle The sac in which an egg develops in the ovary.
Follicle cohort synchronisation In the ovaries a few eggs are maturing at the same time. These eggs are all in a different stage of maturation. If one egg reaches a threshold at the right time in the menstrual cycle, the final maturation process will start and this egg will reach ovulation. For IVF/ICSI cycles it is important that more than one egg reaches this threshold at the same time, so they can be retrieved at once before spontaneous ovulation occurs. This is called synchronisation of the follicle cohort.
Follicle Stimulating Hormone (FSH) A hormone produced and released from the pituitary gland. In women it stimulates the production of oestrogen and follicles in the ovary ready for ovulation.
Gestational sac A fluid-filled structure containing an embryo that develops early in pregnancy, usually within the uterus.
Gonadotrophin Releasing Hormone (GnRH) A substance produced by the hypothalamus (part of the brain) to enable the pituitary gland to secrete LH and FSH.
Gonadotrophins Pituitary hormones FSH and LH which stimulate the ovaries in women.

Human Menopausal Gonadotrophin (hMG) An injectable preparation that is obtained from the urine of menopausal women and has biological activity similar to that of FSH.
Luteal phase The last 14 days of the menstrual cycle.
Luteinising Hormone (LH) A hormone produced and released by the pituitary gland. In women it is responsible for ovulation and progestogen production.
Negative feedback A common regulation mechanism to stabilise the body's internal environment. An example is the temperature control of the human body. When your temperature is too high, the body will react in such a way that you cool down, by opening pores and sweating. In this way the body's temperature will not fluctuate too much. The same kind of mechanism is used to keep hormone values stable. An increase in gonadotrophin values will (through negative feedback) result in fewer GnRH receptors. The binding of GnRH to a GnRH receptor in the pituitary gland will result in the release of gonadotrophins, but with fewer GnRH receptors, the releasing process will be lowered and the gonadotrophin levels in the body will drop.
Oocyte The egg from a woman's ovary.
Ova A woman's reproductive cell, also known as egg or oocyte.
Ovarian Hyperstimulation (OHS) Syndrome A condition that occurs from fertility drugs when a large number of follicles in the ovary are stimulated to develop and ovulate. This stimulation causes an enlargement of the ovaries.
Ovulation The release of an egg/ova from an ovarian follicle.
Ovulation induction Medical procedure to produce ovulation.
Polycystic Ovary Syndrome (PCOS) When a woman has enlarged ovaries with multiple cysts and the surface of the ovary is thickened. The woman may ovulate infrequently or not at all.
Premature LH-surge In a normal menstrual cycle an increase in LH-levels (LH-surge) is needed to start ovulation. In IVF/ICSI cycles it is important that the ovulation does not start before the oocytes are mature enough to be retrieved. A LH-surge that occurs too early is called premature and is an unwanted event in IVF/ICSI cycles.
Recombinant (as in recombinant FSH or rFSH) A naturally occurring hormone which has been made in the laboratory with the use of DNA technology.
Subfertility Failure to achieve pregnancy after at least one year of unprotected coitus.
Ultrasound Radiology sounds waves of a high frequency used to visualise the developing foetus in the uterus to check size, growth and the presence of abnormalities.
All these definitions (except for follicle cohort synchronisation, negative feedback and premature LH-surge) were achieved from the glossary of the MDSG Module 2008.

WHAT'S NEW

Last assessed as up-to-date: 15 November 2008.

Date	Event	Description
20 September 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 1, 2010

Date	Event	Description
16 August 2010	Amended	Minor edits made no change to conclusion
18 December 2008	Amended	Title changed
23 November 2008	Amended	New authors added All aspects of original protocol revised
13 April 2008	Amended	Converted to new review format.
19 May 2006	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Brechtje Smulders and Sanne van Oirschot contributed equally to this review.

Brechtje Smulders drafted the Background and Objectives of the review, and performed the search, selected the studies, extracted and analysed the data, contacted the authors of trials and drafted the Results, Discussion and Authors' conclusions of the review together with Sanne M van Oirschot. BS also drafted half of the tables of Characteristics of included studies and drafted Table 1, Table 2 and Table 3.

Sanne M van Oirschot drafted the Methods of the review, and performed the search, selected the studies, extracted and analysed the data, contacted the authors of trials and drafted the Results, Discussion and Authors' conclusions of the review together with Brechtje Smulders. SvO also drafted half of the tables of Characteristics of included studies and all the tables of Characteristics of excluded studies.

Cindy Farquhar helped to solve differences of opinion as a third review author, commented on the review and helped with drafting the Discussion and Authors' conclusions of the review.

Luk Rombauts acted as a clinical expert and commented on the review.

Jan Kremer acted as a clinical expert and commented on the review.

DECLARATIONS OF INTEREST

Luk Rombauts was the first author of a randomised trial about oral contraceptive pre-treatment (Rombauts 2006). This study was sponsored by Organon/Schering Plough.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Stichting Nijmeegs Universiteitsfonds (SNUF), Netherlands.

Scholarship to support students of the University of Nijmegen to do a study, internship or research outside The Netherlands.

- CVSB (Commissie Voorzieningen Studenten Budget), Netherlands.

Compensation for studying outside The Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The biggest change between the protocol and the review is the formation of different subgroups. In the protocol we described that we would perform subgroup analyses on women's age; poor response; agonist long, short and ultra-short protocol; and the duration of pre-treatment. After regarding the included studies, we thought it would make more sense to perform subgroup analyses on the type of GnRH analogue used in the treatment cycles. After this, we could not perform any more subgroup analysis on the planned subjects, because there were not enough studies per subgroup. Furthermore, we did not perform any sensitivity analyses due to the small number of included studies per subgroup.

Other minor things that we changed in this review was the exclusion of oocyte donors as participants, we rewrote the interventions to make them more understandable, we changed the outcome 'ovarian cysts per woman randomised' to 'number of women with ovarian cysts' and we removed a few items of the data extraction because we thought they were less important. At last, we were unable to perform a funnel plot because of the limited number of included studies to each subgroup.

INDEX TERMS

Medical Subject Headings (MeSH)

Contraceptives, Oral [*administration & dosage]; Estrogens [*administration & dosage]; Fertilization in Vitro [*methods]; Gonadotropin-Releasing Hormone [antagonists & inhibitors]; Live Birth; Ovulation Induction [*methods]; Pregnancy Rate; Progestins [*administration & dosage]; Randomized Controlled Trials as Topic; Sperm Injections, Intracytoplasmic; Treatment Outcome

MeSH check words

Female; Humans; Pregnancy