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Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis (Review)

Sallam HN, Garcia-Velasco JA, Dias S, Arici A, Abou-Setta AM, Jaafar SH

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Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis.
Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004635.
DOI: 10.1002/14651858.CD004635.pub2.

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[Intervention Review]

Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2021.

Citation: Sallam HN, Garcia-Velasco JA, Dias S, Arici A, Abou-Setta AM, Jaafar SH. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD004635. DOI: 10.1002/14651858.CD004635.pub2.

ABSTRACT

Background

Women with endometriosis who are treated with in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) have a lower pregnancy rate compared to women with tubal factor infertility. It has been suggested that the administration of gonadotrophin releasing hormone (GnRH) agonists for a few months prior to IVF or ICSI increases the pregnancy rate.

Objectives

To determine the effectiveness of administering GnRH agonists for three to six months prior to IVF or ICSI in women with endometriosis.

Search methods

We used computer searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the National Research Register (NRR) and the MDSG Specialised Register of controlled trials. We handsearched proceedings of annual meetings of the American Society for Reproductive Medicine (ASRM) and the European Society for Human Reproduction and Embryology (ESHRE). We reviewed lists of references in original research and review articles. We contacted experts in various countries to identify unpublished trials.

Selection criteria

We included randomised controlled trials using any GnRH agonist prior to IVF or ICSI to treat women with any degree of endometriosis diagnosed by laparoscopy or laparotomy

Data collection and analysis

Two independent review authors abstracted data (HNS and JGV). We sent e-mails to investigators to seek additional information. We assessed the validity of each study using the methods suggested in the Cochrane Handbook. The data were checked by the third review author (SD) and any disagreement was resolved by arbitration with the fourth review author (AA). We generated 2 x 2 tables for principal outcome measures. The Peto-modified Mantel-Haenszel technique was used to calculate odds ratios (OR) and assess statistical heterogeneity between studies.

Main results

Three randomised controlled trials (with 165 women) were included. The live birth rate per woman was significantly higher in women receiving the GnRH agonist compared to the control group (OR 9.19, 95% CI 1.08 to 78.22). However, this was based on one trial reporting

"viable pregnancy" only. The clinical pregnancy rate per woman was also significantly higher (three studies: OR 4.28, 95% CI 2.00 to 9.15). The information on miscarriage rates came from two trials with high heterogeneity and, therefore, results of the meta-analysis were doubtful. The included studies provided insufficient data to investigate the effects of administration of GnRH agonists on multiple or ectopic pregnancies, fetal abnormalities or other complications.

Authors' conclusions

The administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy by fourfold. Data regarding adverse effects of this therapy on the mother or fetus are not available at present.

PLAIN LANGUAGE SUMMARY

Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis

Endometriosis is a disease characterised by the presence of endometrial tissue (the lining of the womb) outside the cavity of the womb. Many women with the disease suffer from menstrual pain and some suffer from infertility. Infertile women with endometriosis are often treated with in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) but have a lower chance of becoming pregnant compared to women who are infertile with blocked tubes. It has been suggested that giving GnRH agonists before IVF or ICSI could increase the chances of pregnancy. We have reviewed the literature and found that treating women for three to six months with GnRH agonists before IVF or ICSI increases the odds of clinical pregnancy four-fold. However, at present there is no information on the effect of this treatment on the incidence of ectopic pregnancy, multiple pregnancies or complications arising for the women or their offspring.

BACKGROUND

Assisted reproduction is now an established method for the treatment of infertility in a multitude of clinical conditions, including endometriosis-associated infertility. However, the results of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) for women with endometriosis-associated infertility are conflicting. Some studies reported significantly lower pregnancy and implantation rates in women with endometriosis-associated infertility treated with IVF compared to those with tubal factor or unexplained infertility, or both (Matson 1986; Simon 1994; Arici 1996; Cahill 1997). On the contrary, other studies found no statistically significant differences in the pregnancy and implantation rates between these two groups of women (Mahadevan 1983; Wardle 1985; Frydman 1987; Mills 1992; Inoue 1992; Dmowski 1995; Gerber 1995; Olivennes 1995; Tanbo 1995; Padigas 1996; Huang 1997; Hickman 2002; Suzuki 2005).

A meta-analysis of 22 non-randomised studies reported that the chance of achieving pregnancy was significantly lower for women with endometriosis (odds ratio (OR) 0.56, 95% confidence interval (CI) 0.44 to 0.70) when compared to women with tubal factor infertility (Barnhart 2002). Multifactorial analysis also demonstrated a decrease in fertilization and implantation rates and a significant decrease in the number of oocytes retrieved for women with endometriosis. Pregnancy rates for women with severe endometriosis were significantly lower than for women with mild endometriosis (OR 0.60, 95% CI 0.42 to 0.87).

The lower pregnancy and implantation rates have been blamed on the poor quality of oocytes in women with endometriosis. It has been suggested that this poor quality results in decreased fertilization rates (Mahadevan 1983; Wardle 1985; Mills 1992; Cahill 1997; Hull 1998; Bergendal 1998; Pal 1998; Norenstedt 2001). This in turn results in embryos of lower quality along with a reduced implantation rate, especially in severe endometriosis (O'Shea 1985; Yovich 1985; Matson 1986; Simon 1994; Arici 1996).

The poor quality of the oocytes is thought to result from the altered follicular environment in women with endometriosis (Garrido 2000) and various alterations have been described in these women. These include, when compared to controls, an increase in the progesterone concentration (Pellicer 1998a), an increase in the concentration of the cytokine interleukin-6 (IL-6) (Pellicer 1998b), lower levels of cortisol (Smith 2002) and lower concentrations of insulin-like growth factor-one binding protein (IGFBP-1) in the follicular fluid (Cunha-Filho 2003). An increased expression of tumour necrotizing factor-alpha (TNF-alpha) in the cultured granulosa cells from women with endometriosis was also observed (Carlberg 2000). The rate of apoptosis (cell death) in the granulosa cells obtained from women with endometriosis is also increased (Nakahara 1998; Toya 2000) and this may be mediated by elevated concentrations of soluble Fas ligand in the serum and peritoneal fluid of these women (Garcia-Velasco 2002).

On the contrary, endometrial receptivity does not seem to play a role in the lower pregnancy and implantation rates in women with endometriosis who are treated with IVF (Sung 1997; Hickman 2002). In a cross-over experiment, Pellicer compared fertility parameters in different groups of women receiving donor oocytes (Pellicer 2001). They noted that when donor oocytes came from women without known endometriosis embryo development and implantation rates were similar for women with and without endometriosis. However, when the results of oocyte donation were classified according to the nature of the oocytes donated, women who received embryos derived from oocytes from women with endometriotic ovaries showed a significantly lower implantation rate compared to the controls (Pellicer 2001).

In an attempt to increase pregnancy and implantation rates in women with endometriosis being treated with IVF, various approaches have been proposed to treat the endometriosis prior to assisted conception with various claims of success.

Surgical removal of endometriomas (endometriosis cysts) prior to IVF or ICSI was found to diminish the success rate of assisted reproduction in three non-randomised studies (Gerber 2002; Ho 2002; Aboulghar 2003). In contrast, other non-randomised studies have found that laparoscopic cystectomy (cyst removal) of endometriomas did not diminish the ovarian response for IVF (Canis 2001; Marconi 2002); and similarly, LASER vaporization (cauterization) of the internal wall of endometriomas prior to IVF did not significantly diminish the outcome of IVF (Donnez 2001; Wyns 2003). Finally, in non-randomised studies ultrasound-directed endometriotic cyst aspiration performed prior to IVF was associated with mixed results with some workers reporting significantly higher clinical pregnancy rates per cycle (Dicker 1991) while others reported the opposite (Suganuma 2002). Moreover, endometrial cyst aspiration prior to or during IVF seems to be associated with an increased incidence of infection and tubo-ovarian abscess formation as shown in many observational studies (Padila 1993; Dicker 1993; Yaron 1994; Nargund 1995; Younis 1997; Wei 1998).

Apart from surgical approaches, various medical approaches to improve the results of IVF and ICSI in women with endometriosis have been proposed. In a randomised controlled study Kim found that immunotherapy with corticosteroids improved the clinical pregnancy rate in those women (Kim 1997). In another randomised study treatment with danazol prior to IVF or ICSI was found to increase the pregnancy rate significantly in women with repeated IVF failures (Tei 1998). However, the latter two studies have not been replicated. Various non-randomised studies have also claimed that prolonged treatment with GnRH analogues prior to IVF and ICSI improves the pregnancy and implantation rates (Oehninger 1989; Dicker 1990; Dale 1990; Nakamura 1992; Curtis 1993; Marcus 1994; Chedid 1995; Ruiz-Velasco 1998).

OBJECTIVES

To determine the effectiveness of long-term down-regulation of the pituitary with GnRH agonists versus no long-term down-regulation in women with endometriosis undergoing treatment with IVF or ICSI.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised controlled trial where GnRH agonists were used to down-regulate the hypothalamic-pituitary complex for three months or more prior to IVF or ICSI in women with endometriosis. Cross-over trials would be included only if phase one data could be extracted.

Types of participants

Infertile women diagnosed with endometriosis and treated with IVF or ICSI. The diagnosis of endometriosis must have been based on laparoscopy or laparotomy

Types of interventions

Any type of GnRH agonist preparation used to down-regulate the hypothalamic-pituitary complex for three months or more prior to IVF or ICSI in women diagnosed with endometriosis versus conventional stimulation protocols where no long-term down-regulation was done

Types of outcome measures

The following outcomes were recorded if the information was available:

Primary outcomes

- Birth rate - live birth rate per couple/woman where pregnancy reached at least 24 weeks gestation

Secondary outcomes

- Clinical pregnancy rate per couple/woman: confirmed by visualization of a fetal sac by ultrasound.
- Multiple pregnancy rate: number of twin, triplets or higher order pregnancy (specified if possible) per pregnancy and confirmed by ultrasound or delivery.
- Miscarriage rate: miscarriage (confirmed by ultrasound, pregnancy test or by histology) per pregnant woman.
- Ectopic pregnancy rate: ectopic gestation (confirmed by histology) per couple/woman.
- Fetal abnormalities: number of abnormal babies per pregnant women.
- Dose of follicle-stimulating hormone (FSH) or HMG required.
- Duration of FSH or HMG stimulation (days of stimulation per cycle).
- Number of oocytes retrieved.
- Number of embryos obtained.
- Number of embryos frozen.
- Complication rate: adverse effects associated with the treatment, particularly infection and ovarian hyperstimulation syndrome (OHSS), per woman.

Search methods for identification of studies

All reports (in any language) that described randomised controlled trials in women diagnosed with endometriosis and treated with GnRH agonists to down-regulate the hypothalamic-pituitary complex prior to IVF or ICSI were obtained using the following search strategy.

(1) The Menstrual Disorders and Subfertility Group Specialised Register of controlled trials was searched for any trials with endometriosis in the title, abstract or keyword sections.
(2) The Cochrane Central Register of Controlled trials (CENTRAL) on *The Cochrane Library* 2003, Issue 4 was searched in all fields using the following keywords: endometriosis, GnRH, GnRH agonist.

(3) The following electronic databases were searched see Appendix 1:
MEDLINE (1966 to December 2003);
EMBASE (1980 to December 2003);
Biological Abstracts (1980 to December 2003).

The search was conducted using the Cochrane highly sensitive search strategy and the following key words: endometriosis, GnRH, GnRH agonist. The search was performed on titles, abstracts and keywords of the listed articles.

The MEDLINE and Biological Abstracts databases were searched using the following subject headings and keywords.

(4) The National Research Register (NRR) was searched using the same keywords: endometriosis, GnRH, GnRH agonist.

(5) The citation lists of relevant publications, reviews and included studies were also searched.
(6) The MSD Specialised Register results were searched for any trials on endometriosis as it also handsearches the following journals for RCTs:
Acta Europaea Fertilitatis (1969 to 1989), infertility RCTs only (1990 - ongoing);
American Journal of Reproductive Immunology and Microbiology (1980 to 1990);
Andrologia (1980 to 1990), searched for infertility RCTs only (1991 - ongoing);
Archives of Andrology (1978 to 1992), searched for infertility RCTs only (1993 - ongoing);
Climacteric (1998 - ongoing);
Epidemiology (1990 to 1995);
Fertility and Sterility (1950 - ongoing);
Gynecological Endocrinology (1987 - ongoing);
Gynaecological Endoscopy (1991 - ongoing);
Human Reproduction (1986 - ongoing);
International Journal of Andrology (1978 to 1992), searched for infertility RCTs only (1993 - ongoing);
International Journal of Fertility and Women's Medicine (previously International Journal of Fertility and Menopausal Studies and International Journal of Fertility) (1968 - ongoing);
Journal of Andrology (1980 to 1990), searched for infertility RCTs only (1991 - ongoing);
Journal of Assisted Reproduction and Genetics (formerly Journal of In Vitro Fertilization and Embryo Transfer (1984 to 1991), searched for infertility RCTs only (1993 - ongoing);
Journal of Reproduction and Fertility (1966 to 1990), searched for infertility RCTs only (1992 - ongoing);
Maturitas (1978 - ongoing);
Middle East Fertility Society Journal (1996 - ongoing);
Molecular Reproduction and Development (formerly Gamete Research (1978 to 1990)) (1978 to 1992), infertility RCTs only (1993 - ongoing);
Pediatric Perinatal Epidemiology (1987 to 1995);
Reproduction, Fertility, and Development (formerly Clinical Reproduction & Fertility (1982 to 1990)) (1982 to 1993), searched for infertility RCTs only (1982 - ongoing).

Data collection and analysis

H Sallam and J Garcia-Velasco independently selected the trials to be included in accordance with the mentioned criteria. Disagreements were resolved by consensus or through arbitration by A Arici.

Included trials were analysed for the quality and methodological details outlined below. The information is presented in the table Characteristics of included trials. Excluded trials are detailed in the table Characteristics of excluded trials and the reasons for exclusion are mentioned.

Trial Characteristics
(1) Method of randomisation:
true randomisation (A);
unclear or method not mentioned (B);
not randomised despite report (quasi-randomised) (C).
(2) Study design:
parallel or cross-over design, data from cross-over trials was only included if the first phase data could be extracted;
presence or absence of blinding;
duration of follow up.
(3) Concealment of allocation:
clearly adequate;
unclear;
clearly inadequate.
(4) Study setting:
single-centre or multi-centre;
location;
timing and duration of the trial.
(5) Size of the study:
number of women recruited;
number of women randomised;
number of women excluded;
number of women lost to follow up;
number of women analysed.
(6) Analyses:
whether a power calculation was performed or not;
whether an intention-to-treat analysis was done by the study author, not done by author but possible, not possible or uncertain;
whether a valid analysis on either live birth or pregnancy was done by author, not done but possible, or not possible.
(7) Source of funding.

Characteristics of the study participants
(1) Age
(2) Primary or secondary infertility
(3) Duration of infertility
(4) Method of diagnosis of endometriosis
(5) Stage of endometriosis
(6) Previous treatment (medical or surgical)
(7) Using their own oocytes or donated

Interventions
Data on the intervention being evaluated by the trial
(1) Potential co-interventions:
type of GnRH agonist preparation;
dose of GnRH agonist administered;
method of GnRH agonist administration (that is nasal spray, subcutaneous injection, etc).
(2) Trial characteristics:
number of embryos transferred per cycle;
details of the embryo transfer technique (for example ultrasound-guided, type of catheter, etc);
number of treatment cycles offered.
Outcome measures
(1) Primary outcomes:
birth rate - live birth rate per couple/woman where pregnancy reached at least 24 weeks gestation.
(2) Secondary outcomes
clinical pregnancy rate per couple/woman - confirmed by visualization of a fetal sac by ultrasound;
multiple pregnancy rate - number of twins, triplets or higher order pregnancies (specified if possible) per pregnancy confirmed by ultrasound or delivery;
miscarriage rate - miscarriage (confirmed by ultrasound, pregnancy test or by histology) per pregnant woman;
ectopic pregnancy rate - ectopic gestation (confirmed by histology) per couple/woman;
fetal abnormalities - number of abnormal babies per pregnant woman;
dose of FSH or HMG required;
duration of FSH or HMG stimulation (days of stimulation per cycle);
number of oocytes retrieved;
number of embryos obtained;
number of embryos frozen;
complication rate - adverse effects associated with the treatment, particularly infection and ovarian hyperstimulation syndrome (OHSS) per woman.

Assessment of the quality of trials and data extraction was performed independently by HNS and JGV and checked by SD. Any discrepancies were resolved by consensus with the other review author (AA). If a study appeared to meet the eligibility criteria but had aspects of methodology that were unclear, or the data were in a form unsuitable for meta-analysis, the authors were contacted and additional information on trial methodology or actual original trial data, or both, were sought.

Aspects of the methodological quality of the included trial were tabulated (table of Characteristics of included studies) including use of blinding, use of intention-to-treat analysis, power calculations, numbers lost to follow up, and the criteria for including participants and assessing outcomes. A different table was made for excluded studies (Characteristics of excluded studies) and the reasons of exclusion presented.

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Menstrual Disorders and Subfertility Group. Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points and the overlap in their confidence intervals and, more formally, by checking the results of the chi-squared tests (Breslow-Day test). In case of statistical heterogeneity sources for the heterogeneity were considered and commented on.

If different GnRH agonist preparations had been used, subgroup analysis would have been performed to determine the effect of the type of preparation, dose, duration or method of administration on the outcome measures.

As most of the outcome measures for this review use binary data, the results of each study were expressed as an odds ratio (OR) with 95% confidence intervals (CI) and combined for meta-analysis with RevMan software using the Peto-modified Mantel-Haenszel method with the fixed-effect model. Continuous outcome measures were to be analysed using the appropriate statistical tests (weighted mean difference (WMD) using a fixed-effect model). It is the intention of the reviewers that a new search for RCTs will be performed every two years and the review updated accordingly.

RESULTS

Description of studies

Initially 14 studies were identified but only three studies fulfilled our criteria and were included in this review (Dicker 1992; Rickes 2002; Surrey 2002).

Patient characteristics
In all three included studies endometriosis was diagnosed on the basis of laparoscopy or laparotomy. Studies included 165 women with varying degrees of endometriosis and were all published in English, as full reports. The Dicker 1992 study described endometriosis as severe, Rickes 2002 included women with stage II to IV disease and Surrey 2002 included women with stage I to IV disease.

The mean age of participants ranged from 31 to 33 years (Dicker 1992; Surrey 2002) and the age range was reported as 23 to 40 in Rickes 2002. One trial included women undergoing IVF and ICSI (Rickes 2002) while the other two trials included only IVF (Dicker 1992; Surrey 2002). All included studies had a parallel design.

Interventions
The dose of FSH or HMG used was reported by two studies (Dicker 1992; Surrey 2002) and the duration of FSH administration was reported only by Surrey 2002. The GnRH agonist used was decapeptyl by monthly injections for six months (Dicker 1992), goserelin by monthly injections for five to six months (Rickes 2002) and leuprolide acetate intramuscular injections for three months (Surrey 2002).
Outcomes
Only one study reported viable pregnancies (Dicker 1992). Although no details were given it is reasonable to assume that these pregnancies resulted in live birth. All three studies reported clinical pregnancy, but only one of these reported miscarriages per clinically pregnant woman (Dicker 1992).
None of the studies reported live birth, the number of embryos obtained, the number of embryos frozen, the ectopic pregnancy rate, the multiple pregnancy rate, the fetal abnormality rate or the incidence of complications or adverse effects (for example ovarian hyperstimulation syndrome). The number of oocytes retrieved was reported in two studies (Dicker 1992; Surrey 2002).

Further details about the included studies are provided in the table 'Characteristics of included studies'.

Risk of bias in included studies

The overall methodological risk of bias of included trials was poor as none adhered to the CONSORT statement in full. See Characteristics of included studies.

Method of randomisation
All three studies mentioned the use of a randomisation scheme (Dicker 1992; Rickes 2002; Surrey 2002). In the Dicker 1992 study the randomisation process was simply described as "random and sequential". Attempts to contact the authors for clarification failed and we have assumed that this means that patients were sequentially randomised, that is allocated in sequence (as they were recruited) and at random.

In the Rickes 2002 study 110 women were randomised to treatment or control followed by IVF or ICSI, or intra-uterine insemination (IUI). The 63 women who received IUI were in a particular subgroup which was identifiable prior to randomisation. Therefore, excluding these women should not bias the results and we have decided to include only those participants who underwent IVF or ICSI (according to our inclusion criteria).

Concealment of allocation
None of the studies reported any form of allocation concealment. This casts doubt on whether or not selection bias was present in any of these trials and this must be kept in mind when analysing the results.

Study design
In all three studies no placebo was administered to the control group. Neither women nor physicians were blinded to treatment assignment.
Exclusion criteria were specified in two studies (Rickes 2002; Surrey 2002). In all three studies no sample size calculation was performed but appropriate statistical tests were used.
Intention-to -treat (ITT)
Only one study reported the number of women who dropped out from each group (Rickes 2002). This study used an ITT analysis, including the dropouts as negative outcomes in the analysis. One study (Dicker 1992) reported that a subgroup of women was deleted from the study. No details are given as to whether this deletion took place before or after randomisation and we did not receive clarification from the authors. We have assumed that it took place before randomisation as this subgroup was identifiable at the time of recruitment. In correspondence with the authors of Surrey 2002 we have found that there were no dropouts after treatment was started.

Effects of interventions

Birth rate
The live birth rate per couple/woman was not reported in any of the included studies. However, according to our pre-determined criteria women with a viable pregnancy (at least 24 weeks gestation) were included in this outcome. Dicker 1992 reported 9 viable pregnancies for 67 women with an odds ratio of 9.19 (95% CI 1.08 to 79.22), clearly favouring treatment with GnRH over control.
Clinical pregnancy
The clinical pregnancy rate per woman was reported by the three studies, including 78 pregnancies for 165 women. The pooled odds ratio showed that this was significantly higher in women who received the GnRH agonist compared to the control group (OR 4.28, 95% CI 2.00 to 9.15).

Multiple pregnancy
The multiple pregnancy rate per pregnant woman was not reported by any of the studies.

Miscarriage
The miscarriage rate per clinically pregnant woman was reported only by Dicker 1992 and there was no statistically significant difference between both groups (OR 0.50, 95% CI 0.02 to 10.25). The rate of miscarriages per woman randomised showed no significant difference between groups.
Ectopic pregnancy
The ectopic pregnancy rate per couple/woman was not reported by any of the studies. In correspondence with the authors of Surrey 2002 it was determined that there were no ectopic pregnancies in this study.

Fetal abnormalities
The fetal abnormalities rate per pregnant woman was not reported by any of the studies. In correspondence with the authors of Surrey 2002 it was determined that there were no fetal abnormalities in this study.

Dose of FSH or HMG
The dose of HMG or FSH required was reported by two studies (Dicker 1992; Surrey 2002). Meta-analysis showed that there was no statistically significant difference in the number of ampoules required between women who received the GnRH agonist and those who did not (weighted mean difference 0.34, 95% CI -0.70 to 1.38). There was, however, heterogeneity between the studies (I^2 = 71%) with the individual results suggesting conflicting, although non-significant, effects. This may largely be due to the fact that the treatments delivered were not directly comparable (clinical heterogeneity) as treatment effects and interactions between the drugs delivered in 2002 are likely to differ considerably from those of the drugs delivered 10 years earlier (1992).
Duration of FSH or HMG
The duration of HMG or FSH stimulation was reported by one study (Surrey 2002) and this showed that there was no significant difference between women who received the GnRH agonist compared to those who did not (WMD 0.04, 95% CI -0.15 to 0.23).

Number of oocytes
The number of oocytes retrieved was reported by two studies (Dicker 1992; Surrey 2002). Meta-analysis showed that the number of oocytes retrieved was significantly higher in women who received the GnRH agonist compared to those who did not (WMD 0.94, 95% CI 0.36 to 1.51). However, this effect was almost exclusively due to Dicker 1992 where the treatment was clearly favoured, whereas no significant difference was suggested by Surrey 2002.
It is reasonable to assume that these discrepancies are due to the huge advances in assisted reproductive techniques (ART) in the ten-year period that separates these studies, in particular relating to oocyte retrieval techniques. We would therefore suggest that, for this outcome, these studies are not comparable due to clinical heterogeneity.

Number of embryos obtained and frozen
The number of embryos obtained and the number of embryos frozen were not reported in any of the studies and raw data could not be obtained from the authors.

Complication rate
The incidence of complications or adverse effects associated with the treatment was not reported in any of the studies. In correspondence the authors of Surrey 2002 clarified that they were not aware of any adverse outcomes or complications related to treatment.

As mentioned, there was considerable heterogeneity between the studies, in particular for dose of FSH or HMG and number of oocytes retrieved. Since only two to three studies were involved in the meta-analyses we decided to use the I^2 statistic as an indicator of heterogeneity instead of the chi-squared test, which has low power when the number of included studies is small.

DISCUSSION

Women with endometriosis treated with IVF or ICSI have lower pregnancy rates compared to women with no endometriosis (Barnhart 2002). Many treatment regimens have been suggested prior to performing assisted reproduction for these women. The present review confirms the fact that pretreatment of women with endometriosis with a gonadotrophin releasing hormone (GnRH) agonist for at least three months (and up to six months) prior to IVF or ICSI increases the odds of clinical pregnancy by at least four-fold. We have calculated that in order to elicit an increase in the pregnancy rate from 20% to 40%, accepting an 80% probability of finding a true difference and taking 5% as the level of statistical significance, a study should include a minimum of 79 women in each of its arms. The number of women analysed in this review were 88 participants who received the GnRH agonist and 77 controls.

Although some non-randomised studies have suggested that surgical removal of endometriomas prior to IVF or ICSI may affect the success rates, in this review we have seen that the clinical pregnancy rates obtained by Rickes 2002, where this removal was performed, were similar to those obtained by Surrey 2002 where this was not done.

The improvement in the live birth and clinical pregnancy rates following long-term administration of GnRH agonist prior to IVF or ICSI in women with endometriosis may be due to an improvement in the quality of the oocytes (and hence the embryos) or to an improvement in the uterine receptivity leading to better implantation and diminished loss of very early pregnancies. Two of our selected studies reported no significant difference in the fertilization rate and the cleavage rate between women who received GnRH agonist and those who did not (Dicker 1992; Surrey 2002). These findings point towards the endometrium rather than the oocyte being the cause of diminished pregnancy rates in women with endometriosis. However, these results cannot be relied upon as randomisation of the oocytes was not effected. These findings also contradict those of Pellicer et al (Pellicer 2001) who found that when oocytes retrieved from women without known endometriosis were donated to women with and without endometriosis, embryo development and implantation rates were similar in both groups of women, and that women who received embryos derived from oocytes retrieved from women with endometriotic ovaries had a significantly reduced implantation rate compared to the controls (Pellicer 2001). However, the Pellicer study was also not randomised and future randomised studies are needed to resolve this issue (with randomisation of donated oocytes).

In support of the latter theory, we have found that although there was no statistically significant difference in the dose or duration of HMG required for ovarian stimulation between the treatment and control groups, the number of oocytes retrieved was significantly higher in the GnRH agonist group. This could have led to a higher number of 'good' embryos to choose from as there was no significant difference in the number of embryos replaced in all three studies included in our meta-analysis between the treatment and control groups. This effect may have been particularly important in Dicker 1992 as assisted reproduction therapies would be more dependent of the quality of oocytes then. In the Surrey 2002 study there was no significant difference in the number of oocytes retrieved in the control and treatment groups and this is more likely

to reflect current practice than Dicker 1992. Unfortunately, we could not determine whether the administration of the GnRH agonist increased the number of resulting embryos, due to the absence of the raw data.

In this review it was noticed that the two more recent studies (Rickes 2002; Surrey 2002) reported higher clinical pregnancy rates (75% and 80%, respectively) than the earlier study (Dicker 1992). This is most probably due to the general improvement of the results of assisted reproduction that occurred worldwide along the span of the 10 years difference between the studies (including developments in ICSI), rather than for using the agonist for a shorter period (three months in the Surrey 2002 study versus six months in Dicker 1992 and Rickes 2002) to prevent over-inhibition of the hypothalamic-pituitary complex. However, this point can only be resolved by a randomised study comparing both regimens of therapy.

Another point to notice is that in all studies women in the control group were started on the IVF protocol straight away, whereas women on the treatment group had a period of three to six months of treatment with GnRH agonist prior to starting stimulation for IVF. This may mean that the improved results in the treatment group are not only due to the treatment but may be confounded by the amount of time elapsed since surgery, and the fact that these women may be followed up for longer in the trial (three or six months plus IVF cycles, as opposed to just IVF cycles for women in the control group). A randomised study of GnRH agonist versus placebo before IVF or ICSI would help resolve this issue.

AUTHORS' CONCLUSIONS

Implications for practice

The overall message obtained from these three trials is that the administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy by more than four-fold. The odds of live birth are also improved although, due to the poor quality of the only study reporting this (Dicker 1992), the magnitude of this effect is unreliable. There were no significant differences in the number of FSH or HMG ampoules required between women who received the GnRH agonist and those who did not.

Due to the nature of the studies, information on the number of oocytes retrieved was inconclusive although the most recent study (Surrey 2002) suggests there is no significant difference between groups.

Whether the improvement in the pregnancy rate is due to the production of better oocytes (and hence embryos) or better endometrial receptivity cannot be determined as yet. Similarly, whether this therapy is equally beneficial for mild and severe stages of endometriosis and whether one type of agonist is superior to another cannot be determined from the present studies.

Nevertheless, and based on currently available evidence, women with endometriosis treated with IVF or ICSI should receive GnRH agonist therapy for a minimum of three months prior to the procedure as this will increase the odds of clinical pregnancy by four-fold, bearing in mind that data regarding adverse effects of this therapy on the mother or fetus are not available at present.

Implications for research

More randomised studies are needed as we have only found one properly randomised study which reported the ongoing (viable) pregnancy rate; and this was an old study which used drugs and techniques that do not reflect current practice. Future studies should be conducted on an intention-to-treat basis and report the number of oocytes retrieved, the biochemical (preclinical) pregnancy rate and the miscarriage rate, the live birth rate and clinical pregnancy rate as well as meet all CONSORT requirements. Studies should also report the ectopic pregnancy rate, the multiple pregnancy rate and the presence of any complications to the women or congenital abnormalities in the fetus or newborn, as these four outcomes have not been reported by any randomised study so far. Women should also be stratified according to the stage of endometriosis. Comparisons between different types of GnRH agonists and length of the course of treatment (three versus six months) as well as comparisons using placebo are also needed.

There is also a need for research into the mechanism of action of GnRH agonist leading to these improved pregnancy rates. This will require studies on the quality of the oocytes and endometrial receptivity before and after the therapy. The oocyte donation model is an ideal model for such research, with proper randomisation of donated oocytes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Dicker 1992

Study characteristics	
Methods	Patients randomly and sequentially allocated. Method of randomization not stated. No blinding or placebo. Main outcome measures: ongoing pregnancy rate, clinical pregnancy rate and biochemical pregnancy rate.
Participants	67 infertile women with severe endometriosis (AFS classification) diagnosed by laparoscopy including: 35 women received GnRH agonist and 32 controls. Mean age 32 (SD=4) and 31 years (SD=5).
Interventions	Women in the study group received monthly injections of GnRH agonist, 3.2 mg D-Trp LHRH agonist microcapsules (Decapeptyl, Ferring, Kiel, Germany), for 6 months before IVF; control patients (controls) received no treatment prior to IVF. Controlled ovarian stimulation was achieved by the administration of pure FSH (Metrodin; Serono Laboratories, Randolph, MA, USA) combined with human menopausal gonadotrophin (Pergonal, Serono Laboratories) started on day 3 of the cycle in both groups.
Outcomes	Day 3 FSH, mid luteal phase E2 and progesterone levels, mean number of HMG ampoules, number and classification of oocytes retrieved, fertilization and cleavage rate, rate (incidence) of embryo transfer, preclinical (biochemical) pregnancy rate, clinical pregnancy rate, viable pregnancy rate. No maximum number of cycles is defined in the protocol: the 35 women on the treatment group underwent 48 cycles, whereas the 32 women on the control underwent 51 cycles.

Dicker 1992 *(Continued)*

Notes	Attempted to contact author about this study, no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rickes 2002

Study characteristics

Methods	Computer randomization in blocks of six. Patients allocated to 2 main treatment groups and 4 subgroups based on type of ART and disease stage. Women without fallopian tube disease who had optimum mobility of the tube around the ipsilateral ovary had IUI and were excluded. No blinding.
Participants	110 infertile women with stage II to IV endometriosis, according to the revised ASRM classification, diagnosed by videolaparoscopy and had surgical treatment for the disease, subsequently 55 patients received 6 months of GnRH agonist therapy before ART (28 had IVF/ICSI, 27 had IUI) and 55 received no therapy before ART (19 had IVF/ICSI, 36 had IUI), 10 patients dropped out of the study (3 in the study group and 7 in the control group) but were included in the analysis. Exclusion criteria were lack of desire to conceive, age older than 40 and azoospermia of the male partner (ICSI performed with testicular sperm). There were no significant differences between both groups regarding the mean age, duration of infertility, ratio of primary to secondary infertility, mean stage of endometriosis or mean endometriosis score.
Interventions	Treatment group: monthly injections of goserelin 3.6 mg (Zoladex, AstraZeneca, Wedel, Germany) started 3 days after surgery for a total of 5 to 6 cycles. Ovarian stimulation was started exactly 2 weeks after the last depot injection by giving daily injections of recombinant FSH (Gonal-F; Serono, Rome, Italy), 150 to 300 IU. Control group: down regulation with daily SC injections of 0.1 mg of GnRH agonist (Decapeptyl 0.1; Ferring, Kiel, Germany) started on cycle day 18 and ovarian stimulation (with recombinant FSH) started on day 3 of the new cycle.
Outcomes	Pregnancy rate. A maximum of three IVF/ICSI cycles were included.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Surrey 2002

Study characteristics

Surrey 2002 *(Continued)*

Methods	Multi-center (3 center's) study, computer-generated randomization. Method of allocation concealment not stated. No blinding or placebo.
Participants	51 infertile patients with endometriosis diagnosed by laparoscopy or laparotomy within 60 months of cycle initiation (range 2 to 55 months): 25 received GnRH agonist for 3 months before IVF/ICSI and 26 controls received no GnRH agonist before IVF/ICSI. The authors reported no significant differences between both groups in terms of age, early follicular phase serum FSH or oestradiol level, interval between the most recent surgical intervention and cycle onset, surgical technique used or endometriosis score. However, a significantly greater proportion of women receiving the GnRH agonist had stages III and IV endometriosis (revised ASRM classification) compared to the control group. Exclusion criteria were an early follicular phase serum FSH >12 mIU/ml and evidence of ovarian endometrioma.
Interventions	Study group: IM injections of 3.75 mg luprolide acetate (Lupron Depot, TAP Pharmaceuticals, Waukegan, IL) every 28 days for a total of 3 injections. After 30 to 45 days of the last injection leuprolide acetate (TAP Pharmaceuticals) 0.5 to 1.0 mg/d SC was started and given for 10 days. The dose of GnRh agonist was then reduced to 0.25-0.50 mg/d and gonadotrophin stimulation started. Control group: GnRh agonist started 0.5 - 1.0 mg/d SC during the mid-luteal phase. Once gonadotrophin suppression was confirmed, the dose was reduced to 0.25 to 0.5 mg/d SC and exogenous gonadotrophin stimulation was initiated.
Outcomes	Dose of HMG required, number of days of HMG stimulation, number of oocytes obtained, fertilization rate, number of embryos transferred, ongoing pregnancy rate, implantation rate per cycle started, implantation rate per embryo transfer procedure. Main outcome measures were the clinical pregnancy rate, the implantation rate and the biochemical pregnancy rate. Only one cycle was included for each woman.
Notes	Attempted to contact author about this study. A reply including useful additional information was received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

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

Study	Reason for exclusion
Chedid 1995	Retrospective study
Curtis 1993	Not a randomised controlled trial
Dale 1990	Report of 2 cases
Dicker 1990	Not a randomised controlled trial but patients were used as their own controls
Fabregues 1998	Not a randomised controlled trial, but patients were matched for age, indication and number of attempts

Study	Reason for exclusion
Marcus 1994	Not a randomised controlled trial
Nakagawa 2000	Not a randomised controlled trial
Nakamura 1992	Not a randomised controlled trial
Oehninger 1989	Retrospective study
Ruiz-Velasco 1998	Not a randomised controlled study
Sahebkashaf 2003	Randomised controlled trial but "rapid ICSI" was performed and the embryos were immediately transferred to the fallopian tubes by laparoscopy and not into the uterine cavity (ICSI-ZIFT), without proof of fertilization

DATA AND ANALYSES

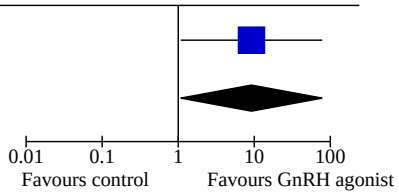
Comparison 1. GnRH agonist versus no agonist before IVF or ICSI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth rate per woman	1	67	Odds Ratio (M-H, Fixed, 95% CI)	9.19 [1.08, 78.22]
1.2 Clinical pregnancy rate per woman	3	165	Odds Ratio (M-H, Fixed, 95% CI)	4.28 [2.00, 9.15]
1.3 Miscarriage rate per clinically pregnant woman	1	14	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.02, 10.25]
1.4 Miscarriage rate per woman randomised	1	67	Odds Ratio (M-H, Fixed, 95% CI)	4.00 [0.42, 37.84]
1.5 Dose of FSH or HMG (ampoules)	2	118	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.70, 1.38]
1.6 Duration of FSH administration (days)	1	51	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.90, 0.98]
1.7 Number of oocytes per woman	2	150	Mean Difference (IV, Fixed, 95% CI)	2.05 [1.27, 2.84]

Analysis 1.1. Comparison 1: GnRH agonist versus no agonist before IVF or ICSI, Outcome 1: Live birth rate per woman

Study or Subgroup	GnRH agonist Events	GnRH agonist Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dicker 1992	8	35	1	32	100.0%	9.19 [1.08 , 78.22]
Total (95% CI)		**35**		**32**	**100.0%**	**9.19 [1.08 , 78.22]**
Total events:	8		1			

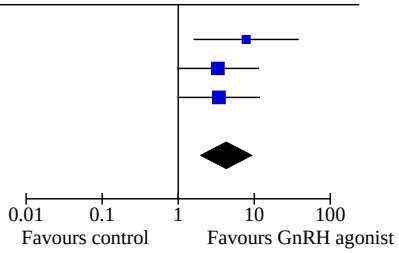
Heterogeneity: Not applicable
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: GnRH agonist versus no agonist before IVF or ICSI, Outcome 2: Clinical pregnancy rate per woman

Study or Subgroup	GnRH agonist Events	GnRH agonist Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dicker 1992	12	35	2	32	20.2%	7.83 [1.59 , 38.47]
Rickes 2002	21	28	9	19	39.4%	3.33 [0.96 , 11.54]
Surrey 2002	20	25	14	26	40.4%	3.43 [0.99 , 11.93]
Total (95% CI)		**88**		**77**	**100.0%**	**4.28 [2.00 , 9.15]**
Total events:	53		25			

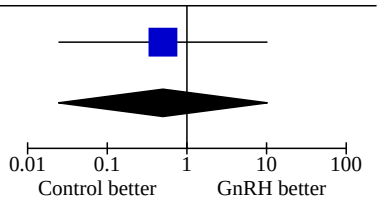
Heterogeneity: $Chi^2 = 0.83$, df = 2 (P = 0.66); $I^2 = 0\%$
Test for overall effect: Z = 3.75 (P = 0.0002)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: GnRH agonist versus no agonist before IVF or ICSI, Outcome 3: Miscarriage rate per clinically pregnant woman

Study or Subgroup	GnRH agonist Events	GnRH agonist Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dicker 1992	4	12	1	2	100.0%	0.50 [0.02 , 10.25]
Total (95% CI)		**12**		**2**	**100.0%**	**0.50 [0.02 , 10.25]**
Total events:	4		1			

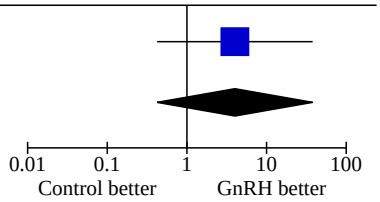
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: GnRH agonist versus no agonist before IVF or ICSI, Outcome 4: Miscarriage rate per woman randomised

Study or Subgroup	GnRH agonist Events	GnRH agonist Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dicker 1992	4	35	1	32	100.0%	4.00 [0.42 , 37.84]
Total (95% CI)		**35**		**32**	**100.0%**	**4.00 [0.42 , 37.84]**
Total events:	4		1			

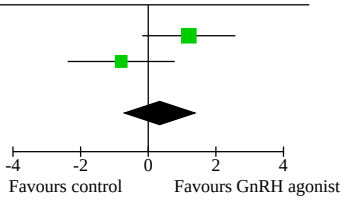
Heterogeneity: Not applicable
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: GnRH agonist versus no agonist before IVF or ICSI, Outcome 5: Dose of FSH or HMG (ampoules)

Study or Subgroup	GnRH agonist Mean	GnRH agonist SD	GnRH agonist Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Dicker 1992	41.8	2.6	35	40.6	3.1	32	56.9%	1.20 [-0.18 , 2.58]
Surrey 2002	42.4	3.21	25	43.2	2.5	26	43.1%	-0.80 [-2.38 , 0.78]
Total (95% CI)			**60**			**58**	**100.0%**	**0.34 [-0.70 , 1.38]**

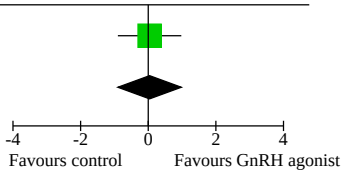
Heterogeneity: Chi² = 3.49, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: GnRH agonist versus no agonist before IVF or ICSI, Outcome 6: Duration of FSH administration (days)

Study or Subgroup	GnRH agonist Mean	GnRH agonist SD	GnRH agonist Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Surrey 2002	10.12	2.15	25	10.08	1.07	26	100.0%	0.04 [-0.90 , 0.98]
Total (95% CI)			**25**			**26**	**100.0%**	**0.04 [-0.90 , 0.98]**

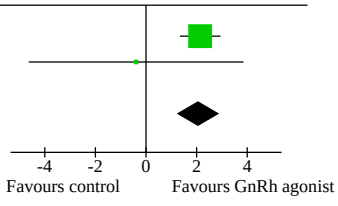
Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.93)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: GnRH agonist versus no agonist before IVF or ICSI, Outcome 7: Number of oocytes per woman

Study or Subgroup	GnRH agonist Mean	GnRH agonist SD	GnRH agonist Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Dicker 1992	5.22	2.22	48	3.08	1.81	51	96.6%	2.14 [1.34 , 2.94]
Surrey 2002	14.84	7.5	25	15.23	7.96	26	3.4%	-0.39 [-4.63 , 3.85]
Total (95% CI)			**73**			**77**	**100.0%**	**2.05 [1.27 , 2.84]**

Heterogeneity: Chi² = 1.32, df = 1 (P = 0.25); I² = 24%
Test for overall effect: Z = 5.11 (P < 0.00001)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search string

1. randomised controlled trial.pt
2. controlled clinical trial.pt.
3. randomised controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. sexpot clinical trials/
10. (clin$ adj25 trial$).tw.
11. ((singl$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw.
12. placebos/
13. placebo$.tw.
14. random$.tw.
15.research design/
16. or/8-15
17. animal/not (human/ and animal/)
18. 7 or 16
19. 18 not 17
20. Endometriosis/
21. (endometriosis adj25 GnRH).tw.
22. or/20-21
23. 19 and 22

The EMBASE database was searched using the following subject headings and keywords.
1. Controlled study/ or Randomised Controlled Trial/
2. Double Blind Procedure/
3. Single Blind Procedure/
4. Crossover Procedure/
5. Drug Comparison/
6. Placebo/
7. Random$.tw.
8. Blatin square.tw.
9. crossover.tw.
10. cross-over.tw.
11. placebo$.tw.
12. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
13. (comparativ$ adj5 trial$).tw.
14. (clinical adj5 trial$).tw.
15. animal/ not (human/ and animal)
16. or/1-14
17. 16 not 15
18. Endometriosis/
19. (endometriosis adj25 GnRH).tw.
20. or/18-19
21. 17 and 20

WHAT'S NEW

Date	Event	Description
19 January 2021	Review declared as stable	No new studies identified or expected

HISTORY

Protocol first published: Issue 1, 2004
Review first published: Issue 1, 2006

Date	Event	Description
12 November 2008	Amended	Converted to new review format.
17 October 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Hassan Sallam: took the lead in writing the protocol; and developed the selection criteria, methods and background as well as the search strategy.
Juan Garcia-Velasco: initiated the protocol, developed the initial objectives, contributed to the background section and the initial extraction of information from trials.

Sofia Dias: reassessed the quality of the trials and performed the statistical analysis.

Aydin Arici: conceptualised the protocol, contributed to the selection criteria, and commented on the draft.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Drug Administration Schedule; Endometriosis [*complications]; Fertility Agents, Female [*administration & dosage]; *Fertilization in Vitro; Gonadotropin-Releasing Hormone [*administration & dosage]; Pituitary Gland [*drug effects]; Pregnancy Outcome; *Sperm Injections, Intracytoplasmic

MeSH check words

Female; Humans; Pregnancy