Cochrane Library

Cochrane Database of Systematic Reviews

Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI (Review)

Kalampokas T, Pandian Z, Keay SD, Bhattacharya S

Kalampokas T, Pandian Z, Keay SD, Bhattacharya S.
Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI.
Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD004752.
DOI: 10.1002/14651858.CD004752.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI

Theodoros Kalampokas[1], Zabeena Pandian[2], Stephen D Keay[3], Siladitya Bhattacharya[2]

[1]Assisted Reproduction Unit, University of Aberdeen, Aberdeen, UK. [2]Obstetrics and Gynaecology, Aberdeen Maternity Hospital, Aberdeen, UK. [3]Centre for Reproductive Medicine, UHCW NHS Trust, Coventry, UK

Contact: Zabeena Pandian, Obstetrics and Gynaecology, Aberdeen Maternity Hospital, Foresterhill, Aberdeen, AB25 2ZD, UK. pandianzl@aol.com, ogy211@abdn.ac.uk.

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 5, 2017.

Citation: Kalampokas T, Pandian Z, Keay SD, Bhattacharya S. Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD004752. DOI: 10.1002/14651858.CD004752.pub2.

ABSTRACT

Background

Ovarian response to stimulation during in-vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI) plays an important role in determining live birth rates. Adjuvant treatments during ovarian stimulation that have different modes of action have been used to improve ovarian response to stimulation and outcome of IVF. Glucocorticoids (GCs) are a class of steroid hormones that have been used either alone or in combination with other stimulatory regimens in order to improve folliculogenesis and pregnancy rates. However, considerable uncertainty remains over whether administration of glucocorticoid during ovarian stimulation until oocyte recovery is superior to no glucocorticoid in improving live birth rates in women undergoing IVF/ICSI.

Objectives

To determine the safety and effectiveness of systemic glucocorticoids during ovarian stimulation for IVF and ICSI cycles.

Search methods

We searched the Cochrane Gynaecology and Fertility Group Specialised Register, the Cochrane Central Register of Studies Online (CRSO), MEDLINE, Embase, CINAHL and PsycINFO from inception to 10 October 2016. We handsearched reference lists of articles, trial registers and relevant conference proceedings and contacted researchers in the field.

Selection criteria

We included randomised controlled trials (RCTs) comparing adjuvant treatment with systemic glucocorticoids during ovarian stimulation for IVF or ICSI cycles versus no adjuvant treatment.

Data collection and analysis

Two review authors independently selected studies, assessed risk of bias and extracted the data. Our primary outcome was live birth. Secondary outcomes included clinical pregnancy, multiple pregnancy, miscarriage, ovarian hyperstimulation syndrome (OHSS) and side-effects. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) and pooled the data using a fixed-effect model. The quality of the evidence was assessed using GRADE methods.

Main results

Four RCTs were included in the review (416 women). The trials compared glucocorticoid supplementation during IVF stimulation versus placebo. Two of the studies had data in a form that we could not enter into analysis, so results include data from only two trials (310)

women. For the outcome of live birth, data were available for only 212 women, as the larger study had data available from only one study centre.

One of the studies gave inadequate description of randomisation methods, but the other was at low risk of bias in all domains. The evidence was rated as low or very low quality for all outcomes, mainly due to imprecision, with low sample sizes and few events.

There was insufficient evidence to determine whether there was any difference between the groups in live birth rate (OR 1.08, 95% CI 0.45 to 2.58; 2 RCTs, n = 212, I^2 = 0%, *low-quality evidence*). Our findings suggest that if the chance of live birth with placebo is assumed to be 15%, the chance following supplementation would be between 7% and 31%. There was no conclusive evidence of a difference in the clinical pregnancy rate (OR 1.69, 95% CI 0.98 to 2.90; 2 RCTs, n = 310, I^2 = 0%, *low-quality evidence*).The evidence suggests that if the chance of clinical pregnancy with placebo is assumed to be 24%, the chance following treatment with glucocorticoid supplementation would be between 23% and 47%. There was also insufficient evidence to determine whether there was any difference between the groups in multiple-pregnancy rate (OR 3.32 , 95% CI 0.12 to 91.60; 1 RCT , n = 20, *very low-quality evidence*) or miscarriage rate (OR 1.00, 95% CI 0.05 to 18.57; 1 RCT, n = 20, *very low-quality evidence*). Neither of the studies reported OHSS or side-effects.

Authors' conclusions

The safety and effectiveness of glucocorticoid administration in women undergoing controlled ovarian hyperstimulation for IVF/ICSI cycles (until the day of oocyte retrieval) is unclear due to the small number of studies and low event rates. Whilst glucocorticoids possibly increase the clinical pregnancy rate, there may be little or no impact on live birth rate. More research is needed.

PLAIN LANGUAGE SUMMARY

Glucocorticoid supplementation for IVF/ICSI

Review question

Does glucocorticoid supplementation improve outcomes in women undergoing controlled ovarian stimulation during in-vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI) cycles?

We reviewed the evidence on women having a glucocorticoid component added to the usual ovarian stimulation protocols versus those that received only the standard traditional ovarian stimulation protocols.

Background

Ovarian response to stimulation during IVF and ICSI cycles plays an important role in determining live birth rates. Most ovarian stimulation regimens administer a combination of hormones to stimulate the ovaries, suppress the pituitary gland and prevent surges of natural hormones that may be detrimental to egg maturation. Various add-on (adjuvant) treatments during ovarian stimulation have been used in an attempt to improve this process, and it has been suggested that the addition of a glucocorticoid component may improve results.

Study characteristics

We found four randomised controlled trials (RCTs), but useable data were available for only two of these. The trials compared adjuvant treatment with systemic glucocorticoids during ovarian stimulation for IVF cycles versus no placebo. The evidence is current to October 2016.

Key results

Two RCTs were included in our analyses (310 women). For the outcome of live birth, data were available for only 212 women, as the larger study had data available from only one study centre.

There was no conclusive evidence of a difference in the primary outcome of live birth rate and the secondary outcome of clinical pregnancy rate. Our findings suggest that if the chance of live birth with placebo is assumed to be 15%, the chance following supplementation would be between 7% and 31%, and that if the chance of clinical pregnancy with placebo is assumed to be 24%, the chance following treatment with supplementation would be between 23% and 47%. There was also insufficient evidence to determine whether there was any difference between the groups in the multiple-pregnancy rate or miscarriage rate. Neither of the studies reported ovarian hyperstimulation syndrome (OHSS) or side-effects.

Thus, the safety and effectiveness of glucocorticoid administration in women undergoing controlled ovarian hyperstimulation for IVF/ICSI cycles (until the day of oocyte retrieval) is unclear due to the small number of studies and low event rates. Whilst glucocorticoids possibly increase the clinical pregnancy rate, there may be little or no impact on the live birth rate.

Quality of the evidence

The evidence was rated as low or very low quality for all outcomes, mainly due to imprecision, with low sample sizes and few events.

Summary of findings for the main comparison. Glucocorticoid supplementation versus placebo for IVF or ICSI

Glucocorticoid supplementation versus placebo for IVF or ICSI

Patient or population: Patients undergoing IVF or ICSI
Settings: Infertility clinics in University/Teaching hospitals
Intervention: Glucocorticoid supplementation during ovarian stimulation
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Glucocorticoid supplementation				
Live birth rate	**147 per 1000**	**157 per 1000** (72 to 308)	**OR 1.08** (0.45 to 2.58)	212 (2 studies)	⊕⊕⊖⊖ **low** [1]	
Clinical pregnancy rate per woman/couple	**236 per 1000**	**343 per 1000** (233 to 473)	**OR 1.69** (0.98 to 2.90)	310 (2 studies)	⊕⊕⊖⊖ **low** [1]	
Multiple pregnancy rate per woman/couple	Only one event (in the glucocorticoid group)		**OR 3.32** (0.12 to 91.60)	20 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	
Miscarriage rate per woman	See footnote[3]		**OR 1.00** (0.05 to 18.57)	20 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	
OHSS per woman	Not reported in the included studies					
Side-effects per woman	Not reported in the included studies					

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

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

[1] Downgraded two levels for very serious imprecision: low number of events and wide confidence intervals
[2] Downgraded one level for serious risk of bias: method of sequence generation not described
[3] Data supplied by trial authors were incomplete. They reported 3 clinical pregnancies and 2 live births in each group, and one miscarriage in the placebo group. We decided to impute a second miscarriage, in the glucocorticoid group, although we accept that this could have been a stillbirth.

BACKGROUND

Description of the condition

This review addresses the use of glucocorticoids as an adjuvant treatment during ovarian stimulation for subfertile couples with any cause of infertility undergoing in-vitro fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI).

Ovarian response to stimulation during IVF and ICSI plays an important role in determining live birth rates.

Most ovarian stimulation regimens employ a combination of exogenous gonadotrophins and a gonadotrophin-releasing agonist (GnRH-a) or antagonist (GnRH antagonist). It is common practice to combine gonadotrophins with a GnRH-a to suppress the pituitary gland and prevent endogenous luteinizing hormone (LH) secretion during ovarian stimulation as LH elevation in the follicular phase is detrimental to egg maturation. More recently, GnRH antagonist preparations have been used as an alternative to GnRH-a. GnRH antagonists have an immediate suppressive effect on the pituitary gland in contrast to the agonists that have an initial "flare-up" effect on follicle-stimulating hormone (FSH) and LH secretion before suppression occurs.

Between 9% and 26% of treatment cycles respond poorly to ovarian stimulation (Keay 1997). The effectiveness of interventions aimed at improving ovarian response to stimulation has been evaluated in several trials (Tarlatzis 2003). Randomised controlled trials (RCTs) have shown little or no benefit in increasing the strength of gonadotrophin stimulation or the use of recombinant FSH to overcome poor ovarian response (Tarlatzis 2003). Improving ovarian responsiveness by reducing the dosage of GnRH-a or using GnRH antagonist instead of GnRH-a has not been adequately evaluated in the context of RCTS. The effectiveness of natural cycle IVF has also been poorly studied.

Adjuvant treatments during ovarian stimulation that have different modes of action has been used to improve ovarian response to stimulation and outcome of IVF. The effectiveness of adjuvant treatment with aspirin (Khairy 2007), growth hormone (Howles 1999), nitric oxide (Battaglia 1999) and steroids (Keay 2002; Miell 1993) have not been adequately evaluated.

Description of the intervention

Glucocorticoids (GCs) are a class of steroid hormones secreted by the adrenal cortex in response to adrenocorticotropic hormone (ACTH) from the anterior pituitary. Cortisol (or hydrocortisone) is the most important human glucocorticoid. Glucocorticoids can be natural (cortisol) or synthetic (dexamethasone, hydrocortisone, prednisolone, methylprednisolone and 16-methyl prednisolone). They differ in the pharmacokinetics (absorption factor, half-life, volume of distribution, clearance), and in pharmacodynamics (for example, the capacity of retention of sodium (Na+) and water).

Despite the side-effects of steroid therapy (hypertension, hypernatraemia (high sodium content in the blood) and water retention, hypokalaemia (low potasium content in the blood), diabetes, osteoporosis, proximal myopathy, psychosis and peptic ulceration), which are largely dose- and duration-dependent, the adjuvant use of glucocorticoids during ovarian stimulation has been reported to be effective in improving ovarian response, reduce cycle cancellation rates (Keay 1997; Singh 1992; Trott 1996), and improve IVF outcome. The overall cost of the treatment cycle may also be lower, due to reduction in the amount of gonadotropins required.

Glucocorticoids have been used either alone (Duvan 2006; Greenblatt 1956), in combination with clomiphene citrate (Daly 1984; Diamant 1981; Elnashar 2006; Kemeter 1986; Lobo 1982; Singh 1992; Trott 1996), or in combination with human menopausal gonadotropins (hMG) (Bider 1996; Bider 1997a), to improve folliculogenesis and pregnancy rates.

Although most studies have been of women with polycystic ovarian disease (PCOS) who were hyper androgenic (exhibiting higher levels of testosterone and related hormones) (Evron 1983; Vanky 2004) treated with clomiphene (CC), the use of steroids has also been reported to improve ovarian response in women with normal androgen levels (normoandrogenic) (Elnashar 2006; Singh 1992; Trott 1996).

How the intervention might work

High androgen levels, regardless of their origin, are detrimental to normal folliculogenesis. Natural (for example, cortisol) and synthetic (for example, prednisolone or dexamethasone) glucocorticoids suppress androgens levels by acting on ovaries, adrenal and pituitary glands, improve follicle development and increase production of growth factors, such as insulin-like growth factor I (IGF-I), which is known to amplify the action of gonadotropins (Langford 1993; Miell 1993). In natural cycles, higher follicular fluid cortisol:cortisone ratios have been found in pregnancy cycles compared to non-pregnancy cycles (Keay 2002). Immediately prior to ovulation a significant rise in follicular cortisol occurs, suggesting this steroid may exert a physiological role in final egg maturation and ovulation (Andersen 1994; Harlow 1997). Glucocorticoids also induce changes in cytokine levels that may be an important determinant in a woman's response to ovarian stimulation (Mathur 1997).

Why it is important to do this review

The concept of adjuvant therapy with glucocorticoid during ovarian stimulation is not new. However, there remains considerable uncertainty over whether administration of glucocorticoid during ovarian stimulation until oocyte recovery is effective and safe in women undergoing IVF/ICSI. Evidence is needed to help inform couples undergoing assisted reproduction, clinicians and policy makers.

OBJECTIVES

To determine the safety and effectiveness of systemic glucocorticoids during ovarian stimulation for IVF and ICSI cycles.

METHODS

Criteria for considering studies for this review

Types of studies

Only parallel, randomised controlled trials (RCTs) , published and unpublished, were considered for inclusion. Quasi-randomised controlled trials were not included.

Types of participants

Inclusion criteria

Subfertile couples with any cause of infertility of at least one year's duration undergoing IVF or ICSI.

Exclusion Criteria

We excluded studies of couples undergoing frozen embryo transfers or oocyte donation cycles.

Types of interventions

Studies had to compare adjuvant systemic (oral or parenteral) administration of glucocorticoids during ovarian stimulation (until day of oocyte recovery) versus no treatment or placebo.

Any dose, timing, length of treatment, route of administration or preparation of glucocorticoids was eligible.

Exclusion Criteria

We excluded studies where the administration of adjuvant glucocorticoids continued throughout ovarian stimulation into the peri-implantation period (following oocyte recovery and embryo transfer), or limited to the peri-implantation period. These interventions are the topic of another published Cochrane review (Boomsma 2012).

Types of outcome measures

Primary outcomes

1. Live birth rate per woman/couple. Live birth is defined as the delivery of one or more living infants.

Secondary outcomes

1. Clinical pregnancy rate per woman/couple. Clinical pregnancy is defined as evidence of pregnancy by clinical or ultrasound parameters (ultrasound visualisation of a gestational sac) includes ectopic pregnancy, though multiple gestational sacs in one patient count as one clinical pregnancy.
2. Multiple pregnancy rate per woman (demonstration of more than one sac with foetal pole on ultrasound scan defines multiple pregnancy).
3. Miscarriage rate per woman.
4. Incidence of ovarian hyperstimulation syndrome (OHSS) per woman. OHSS is a potentially life-threatening adverse effect of ovulation induction. The intravascular depletion associated with OHSS can lead to dehydration, hypovolaemia (low volume of fluid in veins), electrolyte disturbances and thrombosis due to haemoconcentration.
5. Incidence of side-effects from steroids: occurrence per woman of hypertension, hypernatraemia and water retention, hypokalaemia, diabetes, osteoporosis, psychosis, muscle wasting and peptic ulceration.

Search methods for identification of studies

We searched for all relevant published and unpublished RCTs, without language or date restriction and in consultation with the Gynaecology and Fertility Group (CGF) Information Specialist.

Electronic searches

We searched the CGF Trials Register (Appendix 1) from inception to 10 October 2016.

We also searched the following electronic databases;

1. The Cochrane Central Register of Studies Online (CRSO) searched 10 October 2016 (Appendix 2)
2. Ovid MEDLINE from 1946 10 October 2016 (Appendix 3)
3. Ovid Embase from 1980 to 10 October 2016 (Appendix 4)
4. Ovid PsycINFO from 1806 to 10 October 2016 (Appendix 5)
5. Ebsco CINAHL from 1961 to 10 October 2016 (Appendix 6)
6. The trial registers for ongoing trials; The World Health Organization - International Clinical Trials Registry Platform (ICTRP) (Appendix 7), and clinicaltrials.gov (Appendix 8); these web platforms were searched 10 October 2016.

Searching other resources

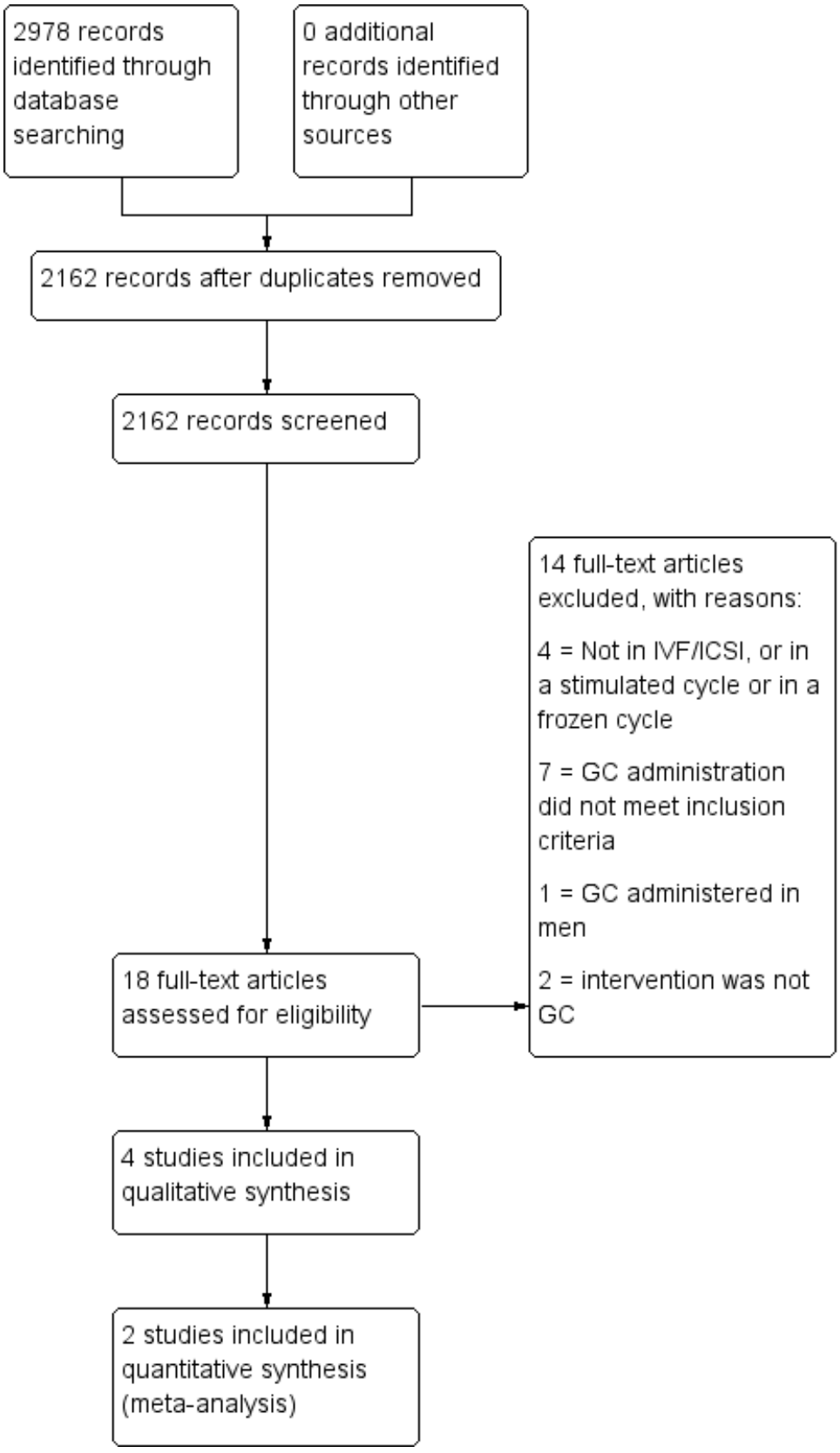
1. We handsearched the following conference proceedings: International Federation of Fertility Societies (IFFS); American Society for Reproductive Medicine (ASRM); British Fertility Society (BFS); and the European Society for Human Reproduction and Embryology (ESHRE) between 1997 and 10 October 2016.
2. We handsearched bibliographies from the identified studies.
3. Where appropriate, we contacted experts and authors in the field.

Data collection and analysis

Selection of studies

After an initial screen of titles and abstracts retrieved by the search, conducted by review authors TK and ZP, we retrieved the full text of all potentially eligible studies. Two review authors (TK, ZP) independently examined these full-text articles for compliance with the inclusion criteria and selected studies eligible for inclusion in the review. We corresponded with study investigators when required, to clarify study eligibility. We documented the selection process with a "PRISMA" flow chart (see Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

All data extraction was independently performed by two review authors (TK, ZP) using forms designed according to Cochrane guidelines. Any discrepancies were resolved by discussion with senior review authors (SK, SB). We sought additional information on trial methodology or actual original trial data from the principal author of trials that appeared to meet the eligibility criteria but were unclear in aspects of methodology, or where the data were in a form unsuitable for meta-analysis.

In the study protocol, we had determined that trials that could not be included in the meta-analysis, due to insufficient data after contacting study authors would be included in the review.

Assessment of risk of bias in included studies

We assessed the included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool for the following domains: sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias. Two review authors (TK, SB) assessed these six domains, with any disagreements resolved by consensus or by discussion with a third review author (ZP). All judgments were fully described. The conclusions are presented in the 'Risk of bias' table and are incorporated into the interpretation of review findings by means of sensitivity analyses (see below).

Measures of treatment effect

For dichotomous data (for example, live birth rates), we used the numbers of events in the control and intervention groups of each study to calculate Mantel Haenszel odds ratios (ORs). We anticipated that all our review outcomes would be reported as dichotomous data. We calculated 95 % confidence intervals (CIs) for all outcomes.

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by Cochrane and found in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 8 (Higgins 2011). The outcome of clinical pregnancy is considered a positive consequence of treatment, therefore a higher proportion of women with a pregnancy is considered a benefit. Whereas, outcomes such as multiple pregnancy are a negative consequence therefore higher numbers are considered to be detrimental. This needs to be taken into consideration when the summary graphs are viewed.

Unit of analysis issues

The primary analysis was per woman randomised. Multiple live births (for example, twins or triplets) were counted as one live birth event. We planned that only first-phase data from cross-over trials would be included; however, no cross-over trials were found during our searches.

Dealing with missing data

The data were analysed on an intention-to-treat (ITT) basis as far as possible, and attempts were made to obtain missing data from the original investigators. Where these were unobtainable, we planned that imputation of individual values would be undertaken for the primary outcome only: live birth would be assumed not to have occurred in participants with an unreported outcome.

For other outcomes, only the available data were analysed. We planned that imputation undertaken would be subjected to sensitivity analysis (see below).

We assessed the included trials to check whether an ITT analysis was performed and if details of dropouts were extractable. If this information could not be extracted, we contacted the principal author of the trial/s. Reminders were sent to authors if there was no reply after four weeks of initial request. A second reminder was sent to authors who had not replied in that time space, after another four weeks. A letter was sent to authors, if they did not reply to the e-mails.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. Statistical heterogeneity was assessed by the I^2 statistic. We planned that an I^2 value greater than 50% would be taken to indicate substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there were 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

The data from included studies were combined using a fixed-effect model in the following comparisons:

1. adjuvant systemic (oral or parenteral) administration of glucocorticoids during ovarian stimulation (until day of oocyte recovery) versus no treatment;
2. adjuvant systemic (oral or parenteral) administration of glucocorticoids during ovarian stimulation (until day of oocyte recovery) versus placebo.

An increase in the odds of a particular outcome, which may be beneficial (for example, live birth) or detrimental (for example, adverse effects), was displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

We intended to perform subgroup analysis where data were available to examine the effect of glucocorticoids within the following subgroups:

1. women who had poor response to previous stimulation with gonadotrophins;
2. when glucocorticoid has been administered in different dosages and timing.

Sensitivity analysis

Sensitivity analyses were conducted for the primary outcome to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

1. eligibility was restricted to studies without high risk of bias;
2. a random-effects model had been adopted;
3. the summary effect measure was risk ratio rather than odds ratio;
4. alternative methods of data imputation had been adopted.

Overall quality of the body of evidence: 'Summary of findings' table

We prepared a 'Summary of findings' table using GRADEPRO software and Cochrane methods (Higgins 2011). This table evaluates the overall quality of evidence for all review outcomes using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality were justified, documented and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Our search strategy identified 2978 potentially eligible reports, of which we screened 2162, after removing duplicates. We discarded 2144 as clearly irrelevant and screened 18 in full text. Four appeared to meet the inclusion criteria (see PRISMA flow chart: Figure 1).

Data from two studies were eligible for inclusion in the meta-analysis (Fridström 1999; Keay 2001), and we included another two studies (Ashrafi 2007; Rein 1996) which had no data available to include. Ashrafi 2007 did not report pregnancy rate, and the data in Rein 1996 were per cycle and not per woman. Attempts to obtain relevant data from the study authors were unsuccessful.

Included studies

Study design and setting

We included four RCTs (Ashrafi 2007; Fridström 1999; Keay 2001; Rein 1996). The following details relate to the two studies with data available for analysis (Fridström 1999; Keay 2001).

Participants

One study (Fridström 1999) included 20 women with polycystic ovarian disease (PCOS) undergoing IVF, whereas the other (Keay 2001) included 290 women undergoing IVF cycles.

Interventions

In Fridström 1999, women were receiving 10 mg of prednisolone daily throughout ovarian stimulation until the day of human chorionic gonadotropin (hCG) administration, whereas in Keay 2001, women were receiving 0.5 mg of dexamethasone daily, until hCG administration. Women in the control groups received placebo, in both studies.

Outcomes

Neither of the studies reported live birth rate as the primary outcome. However, we obtained live birth data after contacting the authors of the studies. Data regarding live birth rates were available for only one study centre in one of the studies (Keay 2001). Therefore, data regarding live birth involved 212 women in total, 107 receiving glucocorticoid supplementation and 105 in the placebo group.

Both studies reported clinical pregnancy rate. Only Fridström 1999 reported miscarriage rate or multiple pregnancy rate.

Excluded studies

We excluded 14 studies, details of which are presented in the Characteristics of excluded studies.

Ongoing studies

We found no ongoing studies eligible for the review (See Appendix 7 for search strategies)

Risk of bias in included studies

See: Risk of bias in included studies; Figure 2; Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

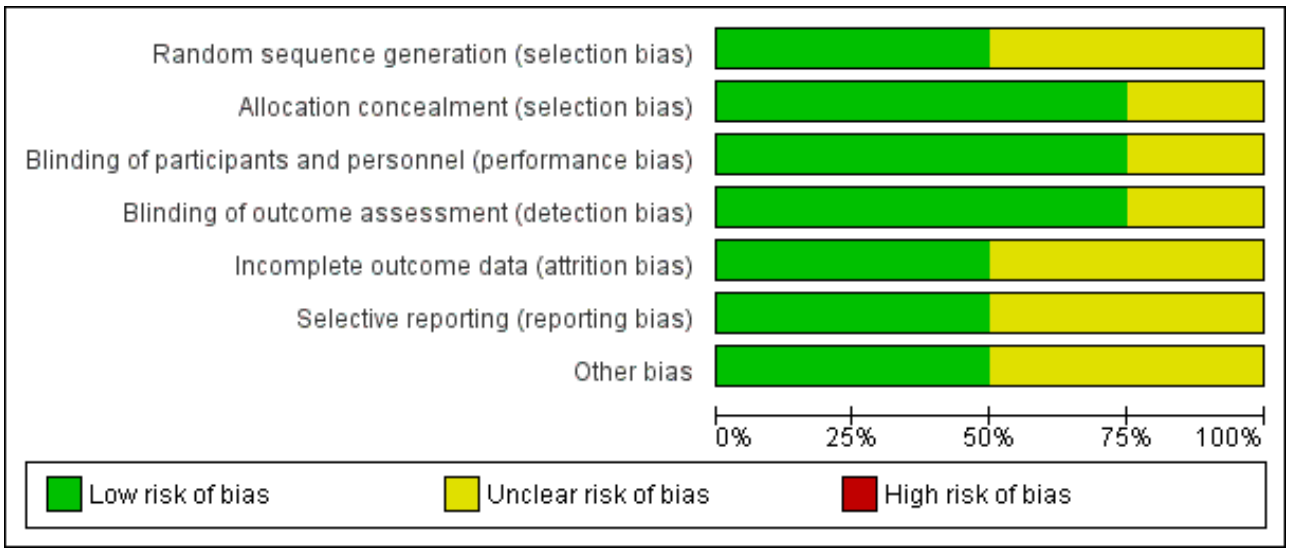
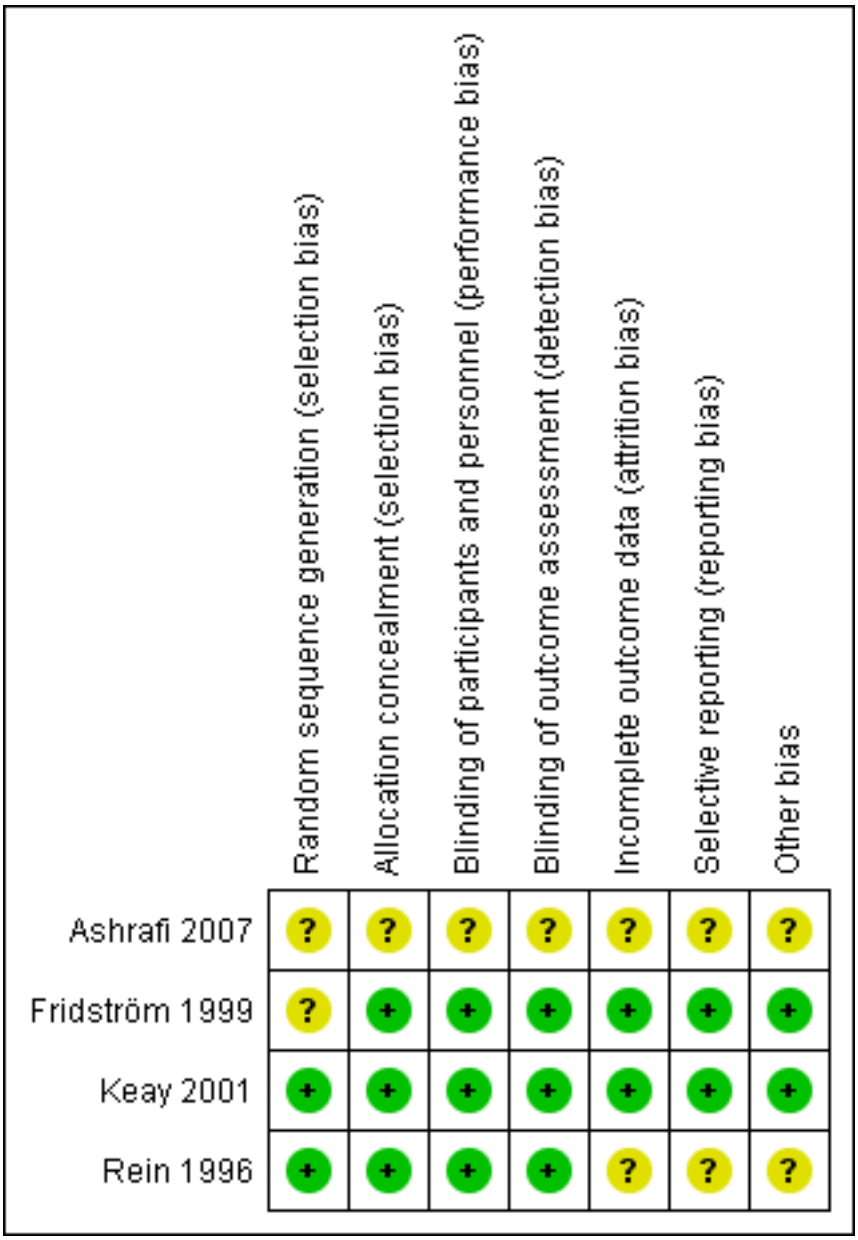


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Two studies were at low risk (Keay 2001; Rein 1996) and two were at unclear risk (Ashrafi 2007; Fridström 1999) of bias related to sequence generation.

Keay 2001 and Rein 1996 used computer-generated blocks from a statistical package . Of the other studies Fridström 1999 did not clearly present the method of randomisation despite stating that women were randomised at down-regulation and Ashrafi 2007 stated that randomised permuted blocks were used but we could not get any further information. Therefore these two studies were rated as at unclear risk of bias.

Allocation concealment

Three studies (Keay 2001; Fridström 1999;Rein 1996) were at low risk of bias for allocation concealment. Ashrafi 2007 did not clearly present exact methodology and we could not get any further information. Thus, that study was rated as at unclear risk of allocation concealment bias.

Blinding

Three studies (Fridström 1999; Keay 2001 ; Rein 1996) were at low risk of performance and detection biases.

In Fridström 1999, women were randomised to receive either prednisolone or placebo from jars coded at the hospital pharmacy and the codes were revealed after treatment of the last patient. In Keay 2001, both participants and staff (clinical and laboratory) were blinded to the choice of either dexamethasone or placebo and the tablets were dispensed in identical containers. In Rein

1996 , the clinical investigators and patients remained blinded throughout the duration of the study and compliance with the study medications was confirmed by the nurse coordinator of the study.

Regarding Ashrafi 2007, it was reported that it was a triple-blind placebo-controlled study but without any further information; thus , it was rated as at unclear risk of blinding bias.

Incomplete outcome data

Two studies (Keay 2001; Fridström 1999) were rated as at low risk of attrition bias. In Keay 2001, data were available for only one study centre for the analysis of life birth (192/192). All randomised women (290/290) were included in analysis for other outcomes in this study. Fridström 1999 excluded one woman from analysis, who did not undergo oocyte retrieval. We assumed that live birth did not occur in this participant; all other women in this study (19/20) were included in analysis.

In the other two studies (Rein 1996; Ashrafi 2007) there is no data available regarding attrition bias; thus, these were rated as at unclear risk .

Selective reporting

Two of the studies (Fridström 1999; Keay 2001) were at low risk of bias related to selective reporting as there was no evidence to suggest that the decision to either publish or fail to publish any specific outcomes by authors of included studies was based on perceived statistical significance.

Data regarding our primary outcome (live birth rate) were obtained after communicating with the authors as the data were not reported in the study publications.

Both studies reported outcomes pre-specified in the methods section.

In the other two studies (Rein 1996 ; Ashrafi 2007) there is no data available regarding reporting bias; thus, these were rated as at unclear risk .

Other potential sources of bias

We found no potential sources of within-study biases in the two studies (Fridström 1999; Keay 2001).

Definitions of clinical pregnancy and live birth were not reported in either of the studies, but were clarified by the authors after communication.

In the other two studies (Rein 1996; Ashrafi 2007) there is no data available regarding any other bias; thus, these were rated as at unclear risk.

Effects of interventions

See: **Summary of findings for the main comparison** Glucocorticoid supplementation versus placebo for IVF or ICSI

1. Glucocorticoid supplementation during IVF/ICSI versus no treatment/placebo

See Summary of findings for the main comparison.

Primary outcome

1.1 Live birth

There was insufficient evidence to determine whether there was any difference between the groups in live birth rate (odds ratio (OR) 1.08, 95% confidence interval (CI)0.45 to 2.58; 2 RCTs, n = 212, I^2 = 0%, *low-quality evidence*). This suggests that if the chance of live birth with placebo is assumed to be 15%, the chance following treatment with glucocorticoid supplementation would be between 7% and 31%.

Secondary outcomes

1.2 Clinical Pregnancy rate

There was no conclusive evidence of a difference between glucocorticoid supplementation and placebo in clinical pregnancy rate (OR 1.69, 95% CI 0.98 to 2.90; 2 RCTs, n = 310, I^2 =0%, *low-quality evidence*). This suggests that if the chance of clinical pregnancy with placebo is assumed to be 24%, the chance following treatment with glucocorticoid supplementation would be between 23% and 47%.

1.3 Multiple-pregnancy rate

Multiple pregnancy rate was reported in only one of the studies (Fridström 1999).

There was insufficient evidence to determine whether there was any difference between the groups in terms of multiple pregnancy rate. Only one event occurred, which was in the glucocorticoid group (OR 3.32 , 95% CI 0.12 to 91.60; 1 RCT , n = 20, *very low-quality evidence*).

1.4 Miscarriage rate

Miscarriage rate was reported in only one of the studies (Fridström 1999).

Data supplied by trial authors were incomplete. They reported three clinical pregnancies and two live births in each group, and one miscarriage in the placebo group. We decided to impute a second miscarriage, in the glucocorticoid group, although we accept that this could have been a stillbirth. There was insufficient evidence to determine whether there was any difference between the groups in terms of miscarriage rate (OR 1.00, 95% CI 0.05 to 18.57; 1 RCT, n = 20, *very low-quality evidence*).

1.5 Ovarian-hyperstimulation syndrome rate

Neither of the studies reported data regarding ovarian hyperstimulation syndrome (OHSS) rate.

1.6. Side-effects

Neither of the studies reported side-effects.

Other analyses

As data were available from only two studies, it was not feasible to construct a funnel plot. Nor were there sufficient data to conduct subgroup analyses. Sensitivity analyses by choice of model or by choice of effect estimate did not alter the main findings. The other planned sensitivity analyses were not conducted because no imputation of data was undertaken and neither study was at high risk of bias in any domain.

DISCUSSION

Summary of main results

Our meta-analysis shows insufficient evidence to determine whether there is any difference in live births between women receiving glucocorticoid supplementation and women receiving placebo.

Furthermore, pooled data from the two trials do not conclusively show an improved clinical pregnancy rate for women receiving glucocorticoid supplementation in comparison with women receiving placebo.

Therefore, there is insufficient evidence to determine the effectiveness of glucocorticoid administration in women undergoing IVF/ICSI cycle.

There was insufficient evidence to determine whether there was any difference between the groups in multiple pregnancy or miscarriage rates, as data were very sparse.

Overall completeness and applicability of evidence

Very few data were available for our primary outcome (live birth rate). Data on adverse events were very limited or absent: multiple pregnancy and miscarriage were only reported by one small study and neither of the studies reported ovarian hyperstimulation syndrome (OHSS) risk and side-effects after glucocorticoid use.

Due to the limited number of studies included in the review, we could not construct a funnel plot and were unable to assess publication bias.

Quality of the evidence

The studies were at low risk of bias in all or nearly all domains. However, the overall quality of the evidence was rated as low or very low due to imprecision, as very few data were available. (See Summary of findings for the main comparison.)

Potential biases in the review process

Methodology implemented from the review authors aimed to ensure that all relevant studies were identified during the search as well as no introduction of biases during the review process.

Agreements and disagreements with other studies or reviews

This is the first Cochrane review examining glucocorticoid use during IVF/ICSI cycles. Tarlatzis and colleagues considered glucocorticoid use in their 2003 review of clinical management of low ovarian response to stimulation for IVF (Tarlatzis 2003). They identified only one randomised controlled trial (RCT) on this topic, which is included in our review, and called for more trials to be conducted.

AUTHORS' CONCLUSIONS

Implications for practice

The safety and effectiveness of glucocorticoid administration in women undergoing controlled ovarian hyperstimulation for IVF/ICSI cycles (until the day of oocyte retrieval) is unclear due to the small number of studies and low event rates. Whilst glucocorticoids possibly increase the clinical pregnancy rate, there may be little or no impact on live birth rate.

Implications for research

A large well-designed randomised controlled trial reporting live birth is needed. It should include assessment of the effects of different glucocorticoid administration protocols, as protocols vary.

ACKNOWLEDGEMENTS

We would like to thank the Cochrane Gynaecology and Fertility Group. In particular, we would like to thank Helen Nagels (Managing Editor) for answering our questions and helping co-ordinate the authors.

REFERENCES

References to studies included in this review

Ashrafi 2007 *{published data only}*

Ashrafi M, Zafarani F, Nejad E, Baghestani AR, Amirchaghmaghi E. Dexamethasone as a supplement for exogenous gonadotropin to improve ovarian response of women over 35 years undergoing IVF/ICSI cycles. *Iranian Journal of Ferility and Sterility* 2007;**1**(2):69-74.

Fridström 1999 *{published data only}*

Fridström M, Carlström K, Sjöblom P, Hillensjö T. Effect of prednisolone on serum and follicular fluid androgen concentrations in women with polycystic ovary syndrome undergoing in-vitro fertilization. *Human Reproduction* 1999;**14**(6):1440-4.

Keay 2001 *{published data only}*

Keay SD, Lenton EA, Cooke ID, Hull MG, Jenkins JM. Low-dose dexamethasone augments the ovarian response to exogenous gonadotrophins leading to a reduction in cycle cancellation rate in a standard IVF programme. *Human Reproduction* 2001;**16**(9):1861-5.

Rein 1996 *{published data only}*

Rein MS, Jackson KV, Sable DB, Thomas PP, Hornstein MD. Dexamethasone during ovulation induction for in-vitro fertilization: a pilot study. *Human Reproduction* 1996;**11**(2):253-5.

References to studies excluded from this review

Badawy 2007 *{published data only}*

Badawy A, Goda H, Ragab A. Induction of ovulation in idiopathic premature ovarian failure: a randomized double-blind trial. *Reproductive Biomedicine Online* 2007;**15**(2):215-9.

Bider 1996 *{published data only}*

Bider D, Menashe Y, Goldenberg M, Dulitzky M, Lifshitz A, Dor J. Dexamethasone as an adjuvant therapy for anovulatory, normoandrogenic patients during ovulation induction with exogenous gonadotropins. *Journal of Assisted Reproduction and Genetics* 1996;**13**(8):613-6.

Bider 1996a *{published data only}*

Bider D, Amoday I, Tur-Kaspa I, Livshits A, Dor J. The addition of a glucocorticoid to the protocol of programmed oocyte retrieval for in-vitro fertilization--a randomized study. *Human Reproduction* 1996;**11**(8):1606-8.

Bider 1996b *{published data only}*

Bider D, Amoday I, Yonesh M, Yemini Z, Mashiach S, Dor J. Glucocorticoid administration during transfer of frozen-thawed embryos: a prospective, randomized study. *Fertility and Sterility* 1996;**66**(1):154-6.

Bider 1997a *{published data only}*

Bider D, Blankstein J, Levron J, Tur-Kaspa I. Gonadotropins and glucocorticoid therapy for "low responders"--a controlled study. *Journal of Assisted Reproduction and Genetics* 1997;**14**(6):328-31.

Bider 1999 *{published data only}*

Bider D, Hourvitz A, Tur Kaspa I, Dirnfeld M, Dor J. Dexamethasone supplementation to gonadotropin stimulation for in vitro fertilization in polycystic ovarian disease. *Journal of Assisted Reproduction and Genetics* 1999;**16**(5):233-5.

Lahteenmaki 1995 *{published data only}*

Lähteenmäki A, Räsänen M, Hovatta O. Low-dose prednisolone does not improve the outcome of in-vitro fertilization in male immunological infertility. *Human Reproduction* 1995;**10**(12):3124-9.

Moffitt 1995 *{published data only}*

Moffitt D, Queenan JT Jr, Veeck LL, Schoolcraft W, Miller CE, Muasher SJ. Low-dose glucocorticoids after in vitro fertilization and embryo transfer have no significant effect on pregnancy rate. *Fertility and Sterility* 1995;**63**(3):571-7.

Mottla 1996 *{published data only}*

Mottla GL, Smotrich DB, Gindoff PR, Stillman RJ. Increasing clinical pregnancy rates after IVF/ET. Can immunosuppression help?. *Journal of Reproductive Medicine* 1996;**41**(12):889-91.

Revelli 2008 *{published data only}*

Revelli A, Dolfin E, Gennarelli G, Lantieri T, Massobrio M, Holte JG, et al. Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study. *Fertility and Sterility* 2008;**90**(5):1685-91.

Tan 1992 *{published data only}*

Tan SL, Balen A, el Hussein E, Campbell S, Jacobs HS. The administration of glucocorticoids for the prevention of ovarian hyperstimulation syndrome in in vitro fertilization: a prospective randomized study. *Fertility and Sterility* 1992;**58**(2):378-83.

Ubaldi 2002 *{published data only}*

Ubaldi F, Rienzi L, Ferrero S, Anniballo R, Iacobelli M, Cobellis L, Greco E. Low dose prednisolone administration in routine ICSI patients does not improve pregnancy and implantation rates.. *Hum Reprod.* 2002;**17**(6):1544-7.

Younis 1992 *{published data only}*

Younis JS, Simon A, Koren R, Dorembus D, Schenker JG, Laufer N. The effect of growth hormone supplementation on in vitro fertilization outcome: a prospective randomized placebo-controlled double-blind study.. *Fertil Steril.* 1992;**58**(3):575-80.

Younis 1993 *{published data only}*

Younis JS, Ezra Y, Brzezinnski A, Fibich T, Schenker JG, Laufer N. The effect of growth hormone on granulosa cell function during in-vitro fertilization. *Human Reproduction* 1993;**8**(10):1588-92.

Additional references

Andersen 1994

Andersen CY, Hornnes P. Intrafollicular concentrations of free cortisol close to follicular rupture. *Human Reproduction* 1994;**9**(10):1944-9.

Battaglia 1999

Battaglia C, Salvatori M, Maxia N, Petraglia F, Facchinetti F, Volpe A. Adjuvant L-arginine treatment for in-vitro fertilization in poor responder patients. *Human Reproduction* 1999;**14**(7):1690.

Boomsma 2012

Boomsma CM, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. *Cochrane Database of Systematic Reviews* 2012, Issue 6. [DOI: 10.1002/14651858.CD005996.pub3]

Daly 1984

Daly DC, Walters CA, Soto-Albors CE, Tohan N, Riddick DH. A randomized study of dexamethasone in ovulation induction with clomiphene citrate. *Fertility and Sterility* 1984;**41**(6):844-8.

Diamant 1981

Diamant YZ, Evron S. Induction of ovulation by combined clomiphene citrate and dexamethasone treatment in clomiphene citrate nonresponders. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 1981;**11**(5):335-40.

Duvan 2006

Duvan CI, Ozmen B, Satiroglu H, Atabekoglu CS, Berker B. Does addition of low-dose aspirin and/or steroid as a standard treatment in nonselected intracytoplasmic sperm injection cycles improve in vitro fertilization success? A randomized, prospective, placebo-controlled study. *Journal of Assisted Reproduction and Genetics* 2006;**23**(1):15-21.

Elnashar 2006

Elnashar A, Abdelmageed E, Fayed M, Sharaf M. Clomiphene citrate and dexamethazone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study. *Human Reproduction* 2006;**21**(7):1805-8.

Evron 1983

Evron S, Navot D, Laufer N, Diamant YZ. Induction of ovulation with combined human gonadotropins and dexamethasone in women with polycystic ovarian disease. *Fertility and Sterility* 1983;**40**(2):183-6.

Greenblatt 1956

Greenblatt RB, BarfielD WE, Lampros CP. Cortisone in the treatment of infertility. *Fertility and Sterility* 1956;**7**(3):203-12.

Harlow 1997

Harlow CR, Jenkins JM, Winston RM. Increased follicular fluid total and free cortisol levels during the luteinizing hormone surge. *Fertility and Sterility* 1997;**68**(1):48-53.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from www.cochrane-handbook.org.

Howles 1999

Howles CM, Loumaye E, Germond M, Yates R, Brinsden P, Healy D, et al. Does growth hormone-releasing factor assist follicular development in poor responder patients undergoing ovarian stimulation for in-vitro fertilization?. *Human Reproduction* 1999;**14**(8):1939-43.

Keay 1997

Keay SD, Liversedge NH, Mathur RS, Jenkins JM. Assisted conception following poor ovarian response to gonadotrophin stimulation. *British Journal of Obstetrics and Gynaecology* 1997;**104**(5):521-7.

Keay 2002

Keay SD, Harlow CR, Wood PJ, Jenkins JM, Cahill DJ. Higher cortisol:cortisone ratios in the preovulatory follicle of completely unstimulated IVF cycles indicate oocytes with increased pregnancy potential. *Human Reproduction* 2002;**17**(9):2410-4.

Kemeter 1986

Kemeter P, Feichtinger W. Prednisolone supplementation to Clomid and/or gonadotrophin stimulation for in-vitro fertilization--a prospective randomized trial. *Human Reproduction* 1986;**1**(7):441-4.

Khairy 2007

Khairy M, Banerjee K, El-Toukhy T, Coomarasamy A, Khalaf Y. Aspirin in women undergoing in vitro fertilization treatment: a systematic review and meta-analysis. *Fertility and Sterility* 2007;**88**(4):822-31.

Langford 1993

Langford KS, Miell JP. The insulin-like growth factor-I/binding protein axis: physiology, pathophysiology and therapeutic manipulation. *European Journal of Clinical Investigation* 1993;**23**(9):503-16.

Lobo 1982

Lobo RA, Paul W, March CM, Granger L, Kletzky OA. Clomiphene and dexamethasone in women unresponsive to clomiphene alone. *Obstetrics and Gynecology* 1982;**60**(4):497-501.

Mathur 1997

Mathur RS, Jenkins JM, Bansal AS. The possible role of the immune system in the aetiopathogenesis of ovarian hyperstimulation syndrome. *Human Reproduction* 1997;**12**(12):2629-34.

Miell 1993

Miell JP, Taylor AM, Jones J, Holly JM, Gaillard RC, Pralong FP, et al. The effects of dexamethasone treatment on immunoreactive and bioactive insulin-like growth factors (IGFs) and IGF-binding proteins in normal male volunteers. *Journal of Endocrinology* 1993;**136**(3):525-33.

Singh 1992

Singh KB, Dunnihoo DR, Mahajan DK, Bairnsfather LE. Clomiphene-dexamethasone treatment of clomiphene-resistant women with and without the polycystic ovary syndrome. *Journal of Reproductive Medicine* 1992;**37**(3):215-8.

Tarlatzis 2003

Tarlatzis BC, Zepiridis L, Grimbizis G, Bontis J. Clinical management of low ovarian response to stimulation for IVF: a systematic review. *Human Reproduction Update* 2003;**9**(1):61-76.

Trott 1996

Trott EA, Plouffe L Jr, Hansen K, Hines R, Brann DW, Mahesh VB. Ovulation induction in clomiphene-resistant anovulatory women with normal dehydroepiandrosterone sulfate levels: beneficial effects of the addition of dexamethasone during the follicular phase. *Fertility and Sterility* 1996;**66**(3):484-6.

Vanky 2004

Vanky E, Salvesen KA, Carlsen SM. Six-month treatment with low-dose dexamethasone further reduces androgen levels in PCOS women treated with diet and lifestyle advice, and metformin. *Human Reproduction* 2004;**19**(3):529-33.

References to other published versions of this review

Pandian 2004

Pandian Z, Keay SD, Bhattacharya S. Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD004752]

CHARACTERISTICS OF STUDIES

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

Ashrafi 2007

Methods	Randomised controlled trial
Participants	72 women undergoing IVF/ICSI cycles
Interventions	1 mg of dexamethasone received daily until the day of oocyte aspiration
Outcomes	Number of retrieved oocytes; number of fertilised and transferred embryos; number of gonadotropin ampoules used; levels of oestradiol on the day of hCG injection
Notes	Neither clinical pregnancy nor live birth rates were reported and we got no response to requests for data and further information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were divided into two groups by Randomised permuted block". No further details, despite our contact with the authors.
Allocation concealment (selection bias)	Unclear risk	No further details, despite our contact with the authors.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"In this randomised,triple-blind placebo controlled trial..". No further details, despite our contact with the authors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"In this randomised,triple-blind placebo controlled trial..". No further details, despite our contact with the authors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No further details, despite our contact with the authors.

Ashrafi 2007 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No further details, despite our contact with the authors.
Other bias	Unclear risk	No further details, despite our contact with the authors.

Fridström 1999

Methods	Randomised controlled trial
Participants	20 women with PCOS undergoing IVF.
Interventions	10 mg of prednisolone administered daily until the day of hCG administration, versus placebo
Outcomes	Live birth rate per woman/couple; clinical pregnancy rate per woman/couple; multiple pregnancy rate per woman; miscarriage rate per woman; OHSS per woman; side-effects per woman.
Notes	Miscarriage data (incomplete) were supplied by trial authors. We imputed one miscarriage in the prednisolone group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized at down-regulation in a double-blind fashion to receive either placebo or prednisolone tablets from jars coded at the hospital pharmacy. The codes were revealed after treatment of the last patient." No further details, despite our contact with the authors.
Allocation concealment (selection bias)	Low risk	10 patients in experimental and 10 patients in the control group; patients were randomised at down-regulation; double-blinding/ "Patients received either placebo or prednisolone from jars coded at the hospital pharmacy. The codes revealed after last patient received treatment." Further detail regarding exact methodology was given after personal communication with corresponding author.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding/patients received either placebo or prednisolone from jars coded at the hospital pharmacy; codes revealed after last patient received treatment. Further detail was given after personal communication with corresponding author.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No detection bias existed, as outcome was assessed in a blinded way. That information was given after personal communication with corresponding author.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One woman in the control group was excluded from the study: "because of monofollicular growth, oocyte retrieval was never performed". Outcomes reported in the study for 19/20 randomised women.
Selective reporting (reporting bias)	Low risk	No selective reporting detected
Other bias	Low risk	No other bias detected

Keay 2001

Methods	Randomised controlled trial
Participants	Women undergoing IVF cycles
Interventions	0.5 mg of dexamethasone versus placebo
Outcomes	Live birth rate per woman/couple (available for one arm of the study); clinical pregnancy rate per woman/couple
Notes	Live birth data supplied by trial author. 192 women, 97 receiving dexamethasone and 95 receiving placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	145 patients in experimental and 145 patients in the control group; "Treatments randomized by computer using statistical package ARCUS; sealed envelopes held in the hospital pharmacies were used; Randomization was in blocks of 100; Patients and staff were blinded to the choice"
Allocation concealment (selection bias)	Low risk	"Randomization was in blocks of 100; Patients and staff were blinded to the choice; Tablets (dexamethasone or placebo) were dispensed in identical containers to the patients; Surplus tablets were returned on completion of the stimulation cycle"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and staff were blinded to the choice; Tablets (dexamethasone or placebo) were dispensed in identical containers to the patients; Surplus tablets were returned on completion of the stimulation cycle"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients and staff were blinded to the choice; Tablets (dexamethasone or placebo) were dispensed in identical containers to the patients; Surplus tablets were returned on completion of the stimulation cycle"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 290 randomised women included in analysis. However, for live birth, data were only available for one study centre (n = 192)
Selective reporting (reporting bias)	Low risk	No reporting bias detected
Other bias	Low risk	No other bias detected

Rein 1996

Methods	Randomised controlled trial
Participants	Women undergoing IVF cycles; 25 women participated, 34 cycles
Interventions	0.5 of dexamethasone versus placebo
Outcomes	number of follicles >12 mm in diameter serum oestradiol concentrations on the day of hCG administration

Rein 1996 *(Continued)*

	number of ampoules of HMG administered number of oocytes retrieved percentage of oocytes fertilised number of embryos transferred implantation rate numbers of clinical pregnancies and live birth pregnancies
Notes	Data per cycle not per woman; no response to our requests for per woman data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization scheme was based on computer-generated permuted blocks ..."
Allocation concealment (selection bias)	Low risk	"Compliance with the study medications was confirmed by our nurse coordinator"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The clinical investigators and patients remained blinded to the treatment group throughout the duration of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The clinical investigators and patients remained blinded to the treatment group throughout the duration of the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Could not get the necessary data from the trial author
Selective reporting (reporting bias)	Unclear risk	Could not get the necessary information from the trial author
Other bias	Unclear risk	Nine patients undergoing a subsequent IVF cycle were crossed over to the other treatment group (unclear how many from each group).

ICSI: intra-cytoplasmic sperm injection
IVF: in-vitro fertilisation
hCG: human chorionic gonadotropin
HMG: human menopausal gonadotropins
OHSS: ovarian hyperstimulation syndrome
PCOS: polycystic ovarian syndrome

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

Study	Reason for exclusion
Badawy 2007	Glucocorticoids used for ovulation induction protocol - not IVF/ICSI
Bider 1996	Glucocorticoids used for ovulation induction protocol - not IVF/ICSI
Bider 1996a	Glucocorticoid administration ended after embryo transfer (that is, after oocyte retrieval)

Study	Reason for exclusion
Bider 1996b	Glucocorticoid administered for frozen embryo transfer cycles
Bider 1997a	Glucocorticoids used for ovulation induction protocol - not IVF/ICSI
Bider 1999	Glucocorticoid administration ended just after embryo transfer (that is, after oocyte retrieval)
Lahteenmaki 1995	Examined administration of prednisolone in men (for male immunological infertility)
Moffitt 1995	Prednisolone administered after oocyte retrieval
Mottla 1996	Glucocorticoid administration began after oocyte recovery
Revelli 2008	Glucocorticoid administration ended just before embryo transfer (that is, after oocyte retrieval)
Tan 1992	Glucocorticoids administered after oocyte retrieval
Ubaldi 2002	Glucorticoid administration continued for 4 weeks
Younis 1992	Examined the role of growth hormone in ovarian stimulation
Younis 1993	Examined the role of growth hormone in ovarian stimulation

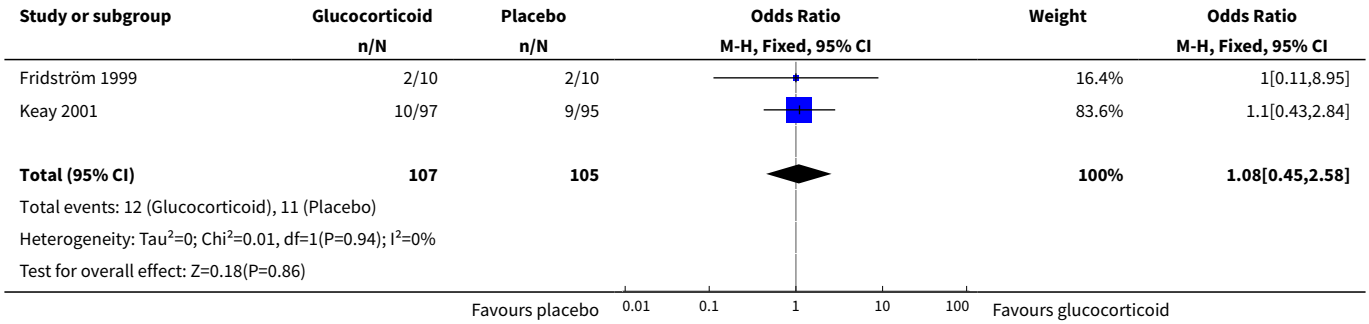
ICSI: intra-cytoplasmic sperm injection
IVF: in-vitro fertilisation

DATA AND ANALYSES

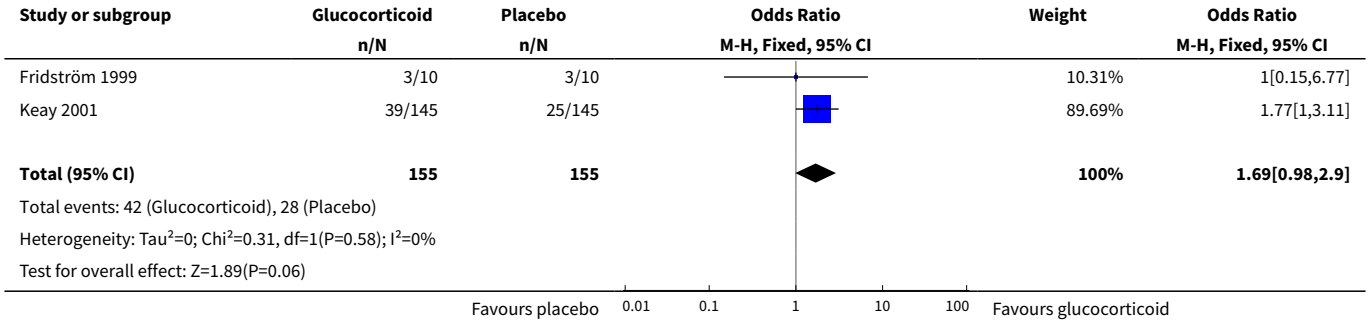
Comparison 1. Glucocorticoid supplementation vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	2	212	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.45, 2.58]
2 Clinical pregnancy rate per woman/couple	2	310	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [0.98, 2.90]
3 Multiple pregnancy rate per woman/couple	1	20	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.12, 91.60]
4 Miscarriage rate per woman	1	20	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.05, 18.57]

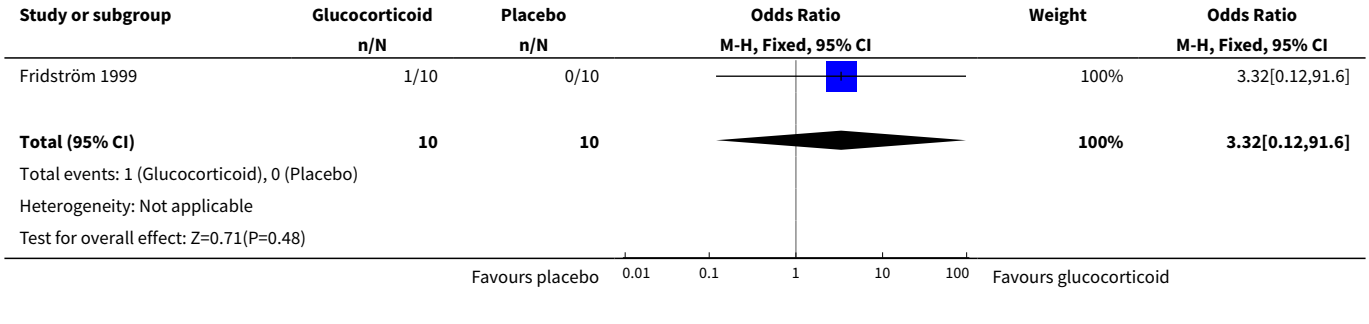
Analysis 1.1. Comparison 1 Glucocorticoid supplementation vs placebo, Outcome 1 Live birth rate.



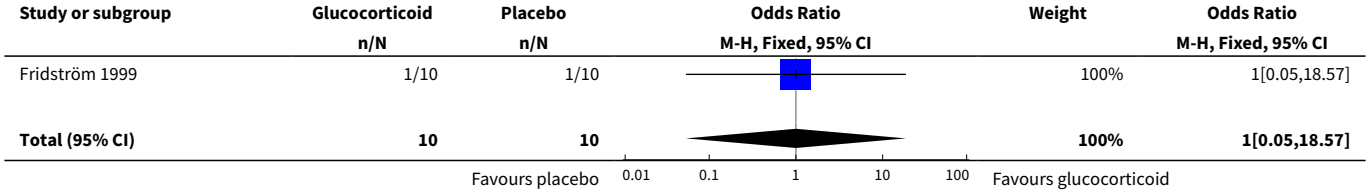
Analysis 1.2. Comparison 1 Glucocorticoid supplementation vs placebo, Outcome 2 Clinical pregnancy rate per woman/couple.

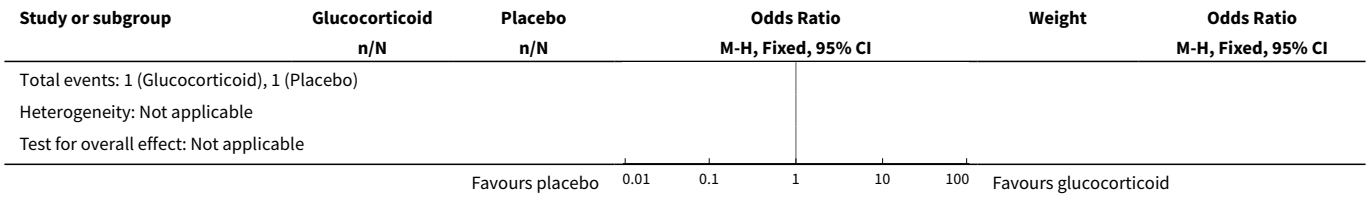


Analysis 1.3. Comparison 1 Glucocorticoid supplementation vs placebo, Outcome 3 Multiple pregnancy rate per woman/couple.



Analysis 1.4. Comparison 1 Glucocorticoid supplementation vs placebo, Outcome 4 Miscarriage rate per woman.





APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group (CGF) search strategy

PROCITE platform

From inception until 10 October 2016

Keywords CONTAINS "Ovulation Induction" or "ovarian hyperstimulation" or "ovarian hyperstimulation syndrome" or "ovarian stimulation" or "Stimulation techniques"or "superovulation" or "superovulation induction" or "ovarian response" or "ovarian responsiveness" or "ovulation" or "ovulation induction" or "ovulation stimulation" or "IVF" or "poor responders" or"poor responder" or"poor prognostic patients" or "Polycystic Ovary Syndrome" or"PCOS" or "in vitro fertilisation" or"in vitro fertilization " or Title CONTAINS "Ovulation Induction" or "ovarian hyperstimulation" or "ovarian hyperstimulation syndrome" or "ovarian stimulation" or "Stimulation techniques"or "superovulation" or "superovulation induction" or "ovarian response" or "ovarian responsiveness" or "ovulation" or "ovulation induction" or "ovulation stimulation" or "IVF" or "poor responders" or"poor responder" or"poor prognostic patients" or "Polycystic Ovary Syndrome" or"PCOS"or "in vitro fertilisation" or"in vitro fertilization "

AND

Keywords CONTAINS "glucocorticoids" or "dexamethasone" or "prednisolone" or "Hydrocortisone"or "methylprednisolone" or "corticosteriods" or "corticosteroids" or "adrenocorticosteroids" or "ACTH" or "Steriods" or"cortisol" or Title CONTAINS "glucocorticoids" or "dexamethasone" or "prednisolone" or "Hydrocortisone"or "methylprednisolone" or "corticosteriods" or "corticosteroids" or "adrenocorticosteroids" or "ACTH" or "Steriods" or"cortisol" (88 hits)

Appendix 2. CENTRAL CRSO search strategy

Web platform

Searched 10 October 2016

#1 MESH DESCRIPTOR ovulation induction EXPLODE ALL TREES 1139

#2 MESH DESCRIPTOR Superovulation EXPLODE ALL TREES 57

#3 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES 1774

#4 MESH DESCRIPTOR Sperm Injections, Intracytoplasmic EXPLODE ALL TREES 445

#5 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES 2704

#6 (ovulat* adj5 induc*):TI,AB,KY 1644

#7 superovulat*:TI,AB,KY 173

#8 (ovar* adj5 induc*):TI,AB,KY 595

#9 (ovar* adj5 stimulat*):TI,AB,KY 1200

#10 (ovulat* adj5 stimulat*):TI,AB,KY 88

#11 (ovar* adj5 respons*):TI,AB,KY 540

#12 (folic* adj5 phase):TI,AB,KY 5

#13 (hyperstimulat* adj5 ovar*):TI,AB,KY 121

#14 (vitro fertili?ation):TI,AB,KY 1858

#15 (ivf or icsi):TI,AB,KY 3362

#16 COH:TI,AB,KY 202

#17 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 5902

#18 MESH DESCRIPTOR Adrenal Cortex Hormones EXPLODE ALL TREES WITH QUALIFIERS AD,AE,PH,TU 14207

#19 MESH DESCRIPTOR Glucocorticoids EXPLODE ALL TREES 13237

#20 MESH DESCRIPTOR Betamethasone EXPLODE ALL TREES 1053

#21 MESH DESCRIPTOR Dexamethasone EXPLODE ALL TREES 2504

#22 MESH DESCRIPTOR Methylprednisolone EXPLODE ALL TREES 1666

#23 MESH DESCRIPTOR Prednisolone EXPLODE ALL TREES 3532

#24 (glucocorticoid* or dexamethasone):TI,AB,KY 10614

#25 Betamethasone:TI,AB,KY 1655

#26 (methylprednisolone* or prednisolone*):TI,AB,KY 7130

#27 (hydrocortisone* or ACTH):TI,AB,KY 8066

#28 (dexol* or deltacortisol*):TI,AB,KY 1

#29 corticotrophin*:TI,AB,KY 130

#30 adrenocorticotroph*:TI,AB,KY 150

#31 corticosteroid*:TI,AB,KY 11446

#32 steroid*:TI,AB,KY 19126

#33 (adrenal cortex hormone*):TI,AB,KY 1880

#34 cortisone*:TI,AB,KY 341

#35 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 48287

#36 #17 AND #35 276

Appendix 3. MEDLINE search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R) 1946-Present

From 1946 to 10th October 2016

1 exp ovulation induction/ or exp superovulation/ (11490)

2 (ovulat$ adj5 induc$).tw. (7982)

3 superovulat$.tw. (3124)

4 (ovar$ adj5 induc$).tw. (8352)

5 (ovar$ adj5 stimulat$).tw. (8197)

6 (ovulat$ adj5 stimulat$).tw. (1291)

7 (ovar$ adj5 response$).tw. (5614)

8 (follic$ adj5 phase$).tw. (8030)

9 (hyperstimulat$ adj5 ovar$).tw. (4535)

10 exp fertilization in vitro/ (30859)

11 vitro fertili?ation.tw. (19430)

12 (ivf or icsi).tw. (22613)

13 COH.tw. (1381)

14 (ovar$ adj5 hyperstimulat$).tw. (4535)

15 or/1-14 (75178)

16 (glucocorticoid$ or dexamethasone$).tw. (95426)

17 Betamethasone.tw. (4267)

18 (methylprednisolone$ or prednisolone$).tw. (35009)

19 (hydrocortisone$ or ACTH$).tw. (51280)

20 (dexol$ or deltacortisol$).tw. (19)

21 corticotrophin$.tw. (3285)

22 adrenocorticotroph$.tw. (2913)

23 corticosteroid$.tw. (87474)

24 steroid$.tw. (205556)

25 adrenal cortex hormone$.tw. (655)

26 cortisone$.tw. (15193)

27 adrenal cortex hormones/ or glucocorticoids/ or exp dexamethasone/ or exp methylprednisolone/ or exp prednisolone/ (185927)

28 or/16-27 (492501)

29 randomized controlled trial.pt. (432794)

30 controlled clinical trial.pt. (91806)

31 randomized.ab. (373468)

32 randomised.ab. (76618)

33 placebo.tw. (185045)

34 clinical trials as topic.sh. (180201)

35 randomly.ab. (265340)

36 trial.ti. (163423)

37 (crossover or cross-over or cross over).tw. (71549)

38 or/29-37 (1126876)

39 exp animals/ not humans.sh. (4325399)

40 38 not 39 (1039139)

41 15 and 28 and 40 (347)

Appendix 4. Embase search strategy

Ovid platform

From 1980 to 10th October 2016

1 exp ovulation induction/ or exp superovulation/ (14893)

2 (ovulat$ adj5 induc$).tw. (9697)

3 superovulat$.tw. (3395)

4 (ovar$ adj5 induc$).tw. (9923)

5 (ovar$ adj5 stimulat$).tw. (11444)

6 (ovulat$ adj5 stimulat$).tw. (1547)

7 (ovar$ adj5 response$).tw. (7445)

8 (follic$ adj5 phase$).tw. (9466)

9 (hyperstimulat$ adj5 ovar$).tw. (6398)

10 exp fertilization in vitro/ (44990)

11 vitro fertili?ation.tw. (24257)

12 (ivf or icsi).tw. (35925)

13 COH.tw. (1918)

14 (ovar$ adj5 hyperstimulat$).tw. (6398)

15 or/1-14 (101425)

16 (glucocorticoid$ or dexamethasone$).tw. (119299)

17 (methylprednisolone$ or prednisolone$).tw. (47659)

18 (hydrocortisone$ or ACTH$).tw. (54281)

19 (dexol$ or deltacortisol$).tw. (33)

20 corticotrophin$.tw. (3561)

21 adrenocorticotroph$.tw. (2864)

22 corticosteroid$.tw. (119151)

23 steroid$.tw. (263844)

24 adrenal cortex hormone$.tw. (327)

25 cortisone$.tw. (10848)

26 exp corticosteroid therapy/ or exp steroid therapy/ (88886)

27 exp glucocorticoid/ct, do, dt, dl, im, na, iv, po, tp, td [Clinical Trial, Drug Dose, Drug Therapy, Intradermal Drug Administration, Intramuscular Drug Administration, Intranasal Drug Administration, Intravenous Drug Administration, Oral Drug Administration, Topical Drug Administration, Transdermal Drug Administration] (314564)

28 exp dexamethasone/cm, dt, th [Drug Comparison, Drug Therapy, Therapy] (52257)

29 16beta methylprednisolone/ or methylprednisolone/ (77997)

30 exp methylprednisolone/ct, dt [Clinical Trial, Drug Therapy] (52005)

31 exp 16beta methylprednisolone/ (21)

32 exp prednisolone/ct, dt, th [Clinical Trial, Drug Therapy, Therapy] (69485)

33 or/16-32 (795845)

34 15 and 33 (7915)

35 Clinical Trial/ (975748)

36 Randomized Controlled Trial/ (453205)

37 exp randomization/ (82914)

38 Single Blind Procedure/ (25985)

39 Double Blind Procedure/ (135375)

40 Crossover Procedure/ (53181)

41 Placebo/ (318874)

42 Randomi?ed controlled trial$.tw. (146432)

43 Rct.tw. (21893)

44 random allocation.tw. (1608)

45 randomly.tw. (334709)

46 randomly allocated.tw. (26257)

47 allocated randomly.tw. (2194)

48 (allocated adj2 random).tw. (839)

49 Single blind$.tw. (18417)

50 Double blind$.tw. (171349)

51 ((treble or triple) adj blind$).tw. (624)

52 placebo$.tw. (245007)

53 prospective study/ (379148)

54 or/35-53 (1934309)

55 case study/ (91348)

56 case report.tw. (319587)

57 abstract report/ or letter/ (979792)

58 or/55-57 (1381716)

59 54 not 58 (1884230)

60 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5695539)

61 59 not 60 (1762326)

62 34 and 61 (799)

Appendix 5. PsycINFO search strategy

Ovid platform

From 1806 until 10 October 2016

1 exp Ovulation/ (345)

2 (ovulat$ adj5 induc$).tw. (113)

3 superovulat$.tw. (6)

4 (ovar$ adj5 induc$).tw. (405)

5 (ovar$ adj5 stimulat$).tw. (140)

6 (ovulat$ adj5 stimulat$).tw. (27)

7 (ovar$ adj5 response$).tw. (200)

8 (follic$ adj5 phase$).tw. (807)

9 (hyperstimulat$ adj5 ovar$).tw. (12)

10 exp Reproductive Technology/ (1587)

11 COH.tw. (88)

12 or/1-11 (3562)

13 (glucocorticoid$ or dexamethasone$).tw. (7795)

14 (methylprednisolone$ or prednisolone$).tw. (803)

15 (hydrocortisone$ or ACTH$).tw. (3657)

16 (dexol$ or deltacortisol$).tw. (3)

17 corticotrophin$.tw. (598)

18 adrenocorticotroph$.tw. (601)

19 corticosteroid$.tw. (2718)

20 steroid$.tw. (8705)

21 adrenal cortex hormone$.tw. (14)

22 cortisone$.tw. (246)

23 exp Adrenal Cortex Hormones/ (13460)

24 exp Glucocorticoids/ (3611)

25 exp Dexamethasone/ (1173)

26 exp Prednisolone/ (172)

27 or/13-26 (28713)

28 12 and 27 (307)

29 random.tw. (47973)

30 control.tw. (372247)

31 double-blind.tw. (20160)

32 clinical trials/ (9902)

33 placebo/ (4685)

34 exp Treatment/ (665205)

35 or/29-34 (1026408)

36 28 and 35 (121)

Appendix 6. CINAHL search strategy

Ebsco platform

From 1961 until 10 October 2016

#	Query	Results
S25	S9 AND S24	106
S24	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	60,022
S23	(MM "Prednisolone+")	1,507
S22	(MM "Methylprednisolone")	822
S21	(MM "Dexamethasone")	1,789
S20	(MM "Glucocorticoids+") OR (MM "Prednisone")	5,820
S19	(MM "Adrenal Cortex Hormones+")	10,505
S18	TX cortisone*	440
S17	TX adrenal cortex hormone*	9,984
S16	TX steroid*	28,711

(Continued)

S15	TX corticosteroid*	10,878
S14	TX adrenocorticotroph*	92
S13	TX corticotrophin*	93
S12	TX hydrocortisone* or TX ACTH*	6,194
S11	TX methylprednisolone* or TX prednisolone*	4,920
S10	TX glucocorticoid* or TX dexamethasone*	11,410
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	1,759
S8	TX (hyperstimulat* N5 ovar*)	395
S7	TX(follic* N5 phase*)	468
S6	TX (ovar* N5 respons*)	281
S5	TX (ovulat* N5 stimulat*)	37
S4	TX(ovulat* N5 induc*)	651
S3	TX superovulation	18
S2	TX ovar* N3 stimulat*	318
S1	(MM "Ovulation Induction")	259

Appendix 7. World Health Organization - International Clinical Trials Registry Platform (ICTRP)

Searched 10th October 2016

Web platform

1."IVF" and "Glucocorticoids"

2."ICSI" and "Glucocorticoids"

3."IVF" and "Prednisolone"

4."ICSI" and "Prednisolone"

5."IVF" and "Dexamethasone"

6."ICSI" and "Dexamethasone"

7."IVF" and "Hydrocortisone"

8."ICSI" and "Hydrocortisone"

Appendix 8. Clinicaltrials.gov

Searched 10th October 2016

Web platform

1."IVF" and "Glucocorticoids"

2."ICSI" and "Glucocorticoids"

3."IVF" and "Prednisolone"

4."ICSI" and "Prednisolone"

5."IVF" and "Dexamethasone"

6."ICSI" and "Dexamethasone"

7."IVF" and "Hydrocortisone"

8."ICSI" and "Hydrocortisone"

WHAT'S NEW

Date	Event	Description
4 May 2017	Review declared as stable	Authors did not identify any ongoing studies relevant to this review. As further studies are unlikely, this review will no longer be updated.

CONTRIBUTIONS OF AUTHORS

Theodoros Kalampokas: Responsible for taking over the review from previous review authors and writing the draft version of the review.

Zabeena Pandian: Responsible for writing the research protocol and revising the final version of the review.

Stephen Keay: Revising the final version of the review.

Siladitya Bhattacharya: Revising the final version of the review.

DECLARATIONS OF INTEREST

TK, ZP, SK and SB have no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- None, Other.

  None

External sources

- None, Other.

  None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methodological update

More precisely, the following sensitivity analyses were added: analyses of the primary outcome using a random-effects model; analyses of the primary outcome where the summary effect measure was risk ratio rather than odds ratio; adoption of alternative methods (described in the appropriate section) of data imputation. The planned sensitivity analysis regarding exclusion of studies with outlying results was removed.

The implementation of "GRADE" and 'Summary of findings' table methodology is a post-protocol addition to meet current Cochrane standards.

We edited the wording in the Data extraction and management section to make clear that studies meeting our inclusion criteria but with no useable data would be included in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Birth Rate; *Fertilization in Vitro; *Sperm Injections, Intracytoplasmic; Glucocorticoids [*administration & dosage] [adverse effects]; Ovulation Induction [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy