Cochrane Library

Cochrane Database of Systematic Reviews

Progestogen for preventing miscarriage (Review)

Haas DM, Ramsey PS

Haas DM, Ramsey PS.
Progestogen for preventing miscarriage.
Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD003511.
DOI: 10.1002/14651858.CD003511.pub3.

www.cochranelibrary.com

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 3
METHODS . . . 3
Figure 1. . . . 7
RESULTS . . . 8
Figure 2. . . . 10
Figure 3. . . . 11
DISCUSSION . . . 14
AUTHORS' CONCLUSIONS . . . 15
ACKNOWLEDGEMENTS . . . 15
REFERENCES . . . 15
CHARACTERISTICS OF STUDIES . . . 18
DATA AND ANALYSES . . . 38
Analysis 1.1. Comparison 1 Progestogen versus placebo/no treatment, Outcome 1 Miscarriage (all trials). . . . 39
Analysis 1.2. Comparison 1 Progestogen versus placebo/no treatment, Outcome 2 Miscarriage (placebo controlled trials only). . . . 40
Analysis 1.3. Comparison 1 Progestogen versus placebo/no treatment, Outcome 3 Miscarriage (women with previous recurrent miscarriage only). . . . 41
Analysis 1.4. Comparison 1 Progestogen versus placebo/no treatment, Outcome 4 Miscarriage (by route of administration versus placebo). . . . 43
Analysis 1.5. Comparison 1 Progestogen versus placebo/no treatment, Outcome 5 Preterm birth. . . . 44
Analysis 1.6. Comparison 1 Progestogen versus placebo/no treatment, Outcome 6 Neonatal death. . . . 45
Analysis 1.7. Comparison 1 Progestogen versus placebo/no treatment, Outcome 7 Fetal genital abnormalities/virilisation. 46
APPENDICES . . . 46
WHAT'S NEW . . . 50
HISTORY . . . 50
CONTRIBUTIONS OF AUTHORS . . . 50
DECLARATIONS OF INTEREST . . . 51
INDEX TERMS . . . 51

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Progestogen for preventing miscarriage

David M Haas[1], Patrick S Ramsey[2]

[1]Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, Indiana, USA. [2]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Uniformed Services University of Health Sciences, Bethesda, MD, USA

Contact address: David M Haas, Department of Obstetrics and Gynecology, Indiana University School of Medicine, 1001 West 10th Street, F-5, Indianapolis, Indiana, IN 46202, USA. dahaas@iupui.edu.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 10, 2013.
Review content assessed as up-to-date: 3 September 2013.

Citation: Haas DM, Ramsey PS. Progestogen for preventing miscarriage. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD003511. DOI: 10.1002/14651858.CD003511.pub3.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Progesterone, a female sex hormone, is known to induce secretory changes in the lining of the uterus essential for successful implantation of a fertilized egg. It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone. Therefore, progestogens have been used, beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriage.

Objectives

To determine the efficacy and safety of progestogens as a preventative therapy against miscarriage.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (1 August 2013), reference lists from relevant articles, attempting to contact authors where necessary, and contacted experts in the field for unpublished works.

Selection criteria

Randomized or quasi-randomized controlled trials comparing progestogens with placebo or no treatment given in an effort to prevent miscarriage.

Data collection and analysis

Two review authors assessed trial quality and extracted data.

Main results

Fourteen trials (2158 women) are included. The meta-analysis of all women, regardless of gravidity and number of previous miscarriages, showed no statistically significant difference in the risk of miscarriage between progestogen and placebo or no treatment groups (Peto odds ratio (Peto OR) 0.99; 95% confidence interval (CI) 0.78 to 1.24) and no statistically significant difference in the incidence of adverse effect in either mother or baby.

A subgroup analysis of placebo controlled trials did not find a difference in the rate of miscarriage with the use of progestogen (10 trials, 1028 women; Peto OR 1.15; 95% CI 0.88 to 1.50).

In a subgroup analysis of four trials involving women who had recurrent miscarriages (three or more consecutive miscarriages; four trials, 225 women), progestogen treatment showed a statistically significant decrease in miscarriage rate compared to placebo or no

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

treatment (Peto OR 0.39; 95% CI 0.21 to 0.72). However, these four trials were of poorer methodological quality. No statistically significant differences were found between the route of administration of progestogen (oral, intramuscular, vaginal) versus placebo or no treatment. No significant differences in the rates of preterm birth, neonatal death, or fetal genital anomalies/virilization were found between progestogen therapy versus placebo/control.

Authors' conclusions

There is no evidence to support the routine use of progestogen to prevent miscarriage in early to mid-pregnancy. However, there seems to be evidence of benefit in women with a history of recurrent miscarriage. Treatment for these women may be warranted given the reduced rates of miscarriage in the treatment group and the finding of no statistically significant difference between treatment and control groups in rates of adverse effects suffered by either mother or baby in the available evidence. Larger trials are currently underway to inform treatment for this group of women.

PLAIN LANGUAGE SUMMARY

Progestogen for preventing miscarriage

We could not find any evidence from randomized controlled trials that progestogen beginning in the first trimester of pregnancy can generally prevent miscarriage.

Hormones called progestogens prepare the womb (uterus) to receive and support the newly fertilized egg. It has been suggested that some women who miscarry may not make enough progesterone in the early part of pregnancy, so supplementing with progesterone has been suggested as a possible way to prevent miscarriage. This review of 14 randomized controlled trials (2158 women) found no evidence that progestogens can prevent miscarriage. No difference in the incidence of adverse effects on either the mother or baby were apparent. There was evidence, however, that women who have suffered three or more miscarriages may benefit from progestogen during pregnancy. Four trials showed a decrease in miscarriage compared with placebo or no treatment in these women, however, the trials were of poorer methodological quality so these findings should be interpreted with caution. No differences were found between the route of administration of progestogen (oral, intramuscular, vaginal) verus placebo or no treatment. More trials are needed and are under way to further clarify the effects in women with multiple prior miscarriages and to further clarify any impact on fetal anomalies.

BACKGROUND

Description of the condition

The term miscarriage refers to the loss of a pregnancy prior to the fetus being viable. Vaginal bleeding during the first 20 weeks of pregnancy, with or without pain, is known as threatened miscarriage. This can present with anything from spots of blood to potentially fatal shock (McBride 1991). Once dilation of the cervix has begun, miscarriage is inevitable (Lede 2005).

Ten per cent to 15% of all clinically recognized pregnancies end in miscarriage (Regan 1989), with 1% to 2% of couples suffering recurrent early losses (traditionally defined as three or more spontaneous miscarriages) (Coulam 1991). It is thought, however, that the true incidence of early spontaneous miscarriage may be much higher (Grudzinskas 1995; Howie 1995; Simpson 1991). Miscarriage is an important cause of morbidity and mortality, especially in low-income countries (Neilson 2006).

It has been estimated that, in over half of miscarriages, a chromosomal abnormality is present (Burgoyne 1991; Szabo 1996). Other risk factors include maternal age greater than 35 years, multiple pregnancies, uterine malformations, polycystic ovaries, autoimmune factors (such as phospholipid antibodies, lupus anticoagulant and cardiolipin antibodies), genetic disorders, poorly controlled diabetes, and having had two or more miscarriages (Lede 2005). For many couples, a cause may never be found.

The occurrence of a miscarriage may induce significant emotional distress in both partners. Initial emotional numbness and denial, anxiety, shock, sense of loss, sadness, emptiness, anger, inadequacy, blame and jealousy, depression, sleep disturbance, social withdrawal, anger and marital disturbance have all been described as emotional responses to pregnancy loss (Atkin 1998; Dyregrove 1987; Vance 1991; Woods 1987).

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

With the development of ultrasound has come the ability to rapidly and accurately establish the viability of a pregnancy, and the technology to predict if a pregnancy is likely to continue when there is bleeding. In situations where ultrasound has been available, the care of women with threatened miscarriage has been rationalized. Attempts to maintain a pregnancy are only likely to be effective if the fetus is viable, and is without chromosomal abnormality (Lede 2005).

Description of the intervention

Progesterone and other progestogens can be given to women orally, vaginally, intramuscularly, or by other routes. Supplementing a pregnancy with progestin often begins early in pregnancy and can continue through the first trimester and beyond.

How the intervention might work

Progesterone, a female sex hormone, is known to induce secretory changes in the lining of the uterus essential for successful implantation of a fertilized egg. It is secreted chiefly by the corpus luteum, a group of cells formed in the ovary after the follicle ruptures during the release of the egg. It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone during the luteal phase of the menstrual cycle and in the early weeks of pregnancy. Therefore, progestogens have been used, beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriage. Their use is particularly common with assisted reproductive technologies.

A review of pregnancy rates following hormonal treatments concluded that the benefits of therapy are uncertain (Karamadian 1992). A 1989 meta-analysis of six trials concluded that exogenous progesterone supplementation after conception does not improve pregnancy outcomes (Goldstein 1989; Regan 1989). It was concluded that low levels of progesterone in early pregnancy reflected an already failed pregnancy (Royal 2001).

Concerns have been raised that the use of progestogens, with their uterine-relaxant properties, in women with fertilized defective ova may cause a delay in spontaneous abortion. Several reports also suggest an association between intrauterine exposure to progesterone containing drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (deformities of the penis or urethra, or both), five to eight per 1000 male births in the general population, may be increased with exposure to these drugs(Briggs 2011). However, some studies do not report increased risk with exposure to these drugs and progesterone supplementation is commonly utilized in assisted reproduction settings. There are insufficient data to quantify the risk to exposed female fetuses. Due to some of these reports and the fact that the urogenital groove is fused by 16 weeks, it has been recommended that progesterone containing drugs be avoided in the first 16 weeks of pregnancy (Briggs 2011).

Why it is important to do this review

Several Cochrane Reviews have been initiated to investigate different interventions for the prevention of miscarriage (Alfirevic 2012; Bamigboye 2003; Lede 2005; Morley 2013; Porter 2006; Rumbold 2011). The aim of this updated review is to study all available data to determine the efficacy and safety of administering prophylactic progesterone in an attempt to prevent pregnancy loss.

OBJECTIVES

To assess the efficacy and safety of progestogens as a preventative therapy against miscarriage.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized trials comparing progestogens with placebo or no treatment, given for the prevention of miscarriage, were eligible for inclusion. Cluster-randomized trials are also eligible for inclusion, but cross-over design trials were not eligible.

Types of participants

Women in the first 20 weeks of pregnancy. No restriction was placed on the age of participants or past obstetric history.

Types of interventions

Progestogen therapy, either natural or synthetic, given prophylactically to prevent miscarriage (i.e. loss during the first 20 weeks of pregnancy) versus placebo therapy or no therapy, regardless of dose, mode of administration or treatment duration. We considered trials pertaining to administration of progestogens starting before pregnancy if treatment continued after pregnancy was confirmed.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Types of outcome measures

Primary outcomes

- Miscarriage

Secondary outcomes

(1) Mother

- Severity of 'morning sickness' - intensified headache, nausea, breast tenderness
- Reported thromboembolic events
- Depression
- Admission to special care unit
- Subsequent fertility

(2) Child

- Preterm birth
- Stillbirth
- Neonatal death
- Low birthweight less than 2500 g
- Fetal genital abnormalities
- Teratogenic effects (impairing normal fetal development)
- Admission to special care unit

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (1 August 2013).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
See Appendix 1 for search methods used in previous versions of this review.

Searching other resources

We searched the citation lists of relevant publications, review articles, abstracts of scientific meetings and included studies for both published and unpublished works.
We contacted experts in the field for unpublished works.
We obtained all reports that described (or may have described) randomized controlled trials of prophylactic progestogen to prevent pregnancy loss. We did not apply any language restrictions and attempted to make to contact authors when additional information was required.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 2.
For this 2013 update, we used the following methods when assessing the reports identified by the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third person.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. We entered data into Review Manager software (RevMan 2012) and checked for accuracy.
When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2011*)*. We resolved any disagreement by discussion or by involving a third assessor.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization; more than 20% missing data);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary Peto Odds Ratio with 95% confidence intervals.

Continuous data

None of our outcomes have continuous data. If future updates add continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomized trials

We did not include cluster-randomized trials in this Review. In future updates, if high-quality cluster-randomized trials are identified, we will consider including them in the analyses along with individually-randomized trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* Section 16.3.4 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit.

Cross-over trials

Cross-over trials are not included as they are inappropriate to the question.

Other unit of analysis issues

If trials with more than two treatment groups are identified and included, we will assess the most appropriate way to include the data. This may be by combining groups to create a pair-wise comparison or to select the most appropriate pair of interventions and exclude the others. No such trials were identified.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomized to each group in the analyses, and all participants were analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

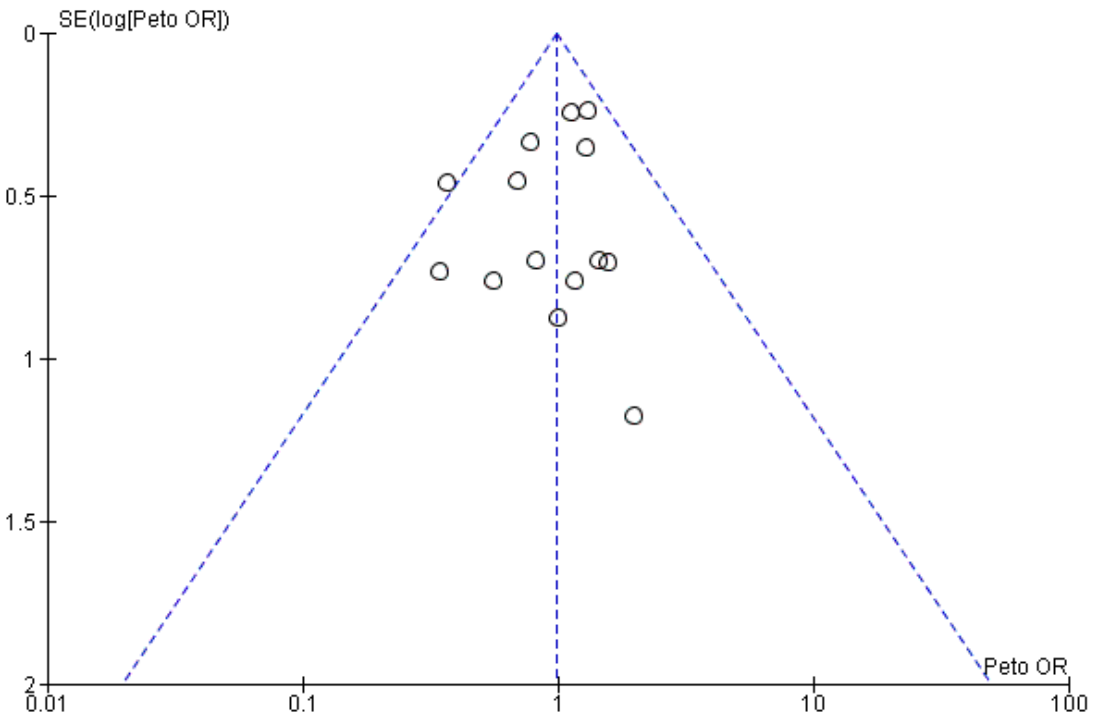
We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

As there were more than 10 studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots, see Figure 1. We assessed funnel plot asymmetry visually. As asymmetry was not suggested by a visual assessment, we did not perform exploratory analyses to investigate it further.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 1. Funnel plot of comparison: 1 Progestogen versus placebo/no treatment, outcome: 1.1 Miscarriage (all trials).



Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful.

In this 2013 update, we used fixed-effect meta-analysis. If in future updates we use random-effects meta-analysis, the random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. The subgroup analyses entailed:

1. placebo controlled trials only versus trials not having placebo control;
2. women who had at least three previous consecutive miscarriages, women with at least two prior miscarriages, versus women in trials not specifying the number of prior miscarriages who present with symptoms of threatened miscarriage;
3. route of administration of progestogen: oral, intramuscular, or vaginal versus placebo;

The following outcome was used in subgroup analysis: miscarriage. We assessed subgroup differences by interaction tests available within RevMan (RevMan 2012). We planned to report the results of subgroup analyses quoting the $\chi 2$ statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We carried out sensitivity analysis to explore the effect of trial quality/risk of bias. This involved analysis of trials based on low

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

risk of bias in order to assess for any substantive difference to the overall results.

RESULTS

Description of studies

Results of the search

See Characteristics of included studies tables for details on all trials identified by the search.

Included studies

Trial design characteristics

Interventions

Route of administration

Five studies administered treatment orally (El-Zibdeh 2005; Goldzieher 1964; Klopper 1965; MacDonald 1972; Moller 1965); four administered treatment intramuscularly (IM) (Le Vine 1964; Nyboe Anderson 2002; Reijnders 1988; Shearman 1963); two used either oral or IM progestogen but did not analyze the groups separately (Berle 1980; Tognoni 1980); two administered treatment via vaginal suppositories (Gerhard 1987; Nyboe Anderson 2002); and one used progestogen pellets inserted into the gluteal muscle (Swyer 1953).

Dosage and type of progestogen

Of the studies that administered treatment orally, one study used a dose of 10 mg/day medroxyprogesterone (Goldzieher 1964), while one study used a staggered dose of medroxyprogesterone (20 mg/day for three days, followed by 10 mg/day for 11 days, then increased the dose two different times later in the study duration) (Moller 1965). One study used a twice daily dose of cyclopentyl enol ether of progesterone (Enol Luteovis) (Klopper 1965), while the last two used 10 mg of oral dydrogesterone either twice daily (El-Zibdeh 2005) or three times daily (MacDonald 1972).

In the four studies that administered treatment IM, two studies used a dose of 500 mg of hydroxyprogesterone caproate (Le Vine 1964; Reijnders 1988), one study used 200 mg natural progesterone for three days followed by 340 mg hydroxyprogesterone caproate twice a week for 11 days (Corrado 2002), while the fourth study used a staggered dose, also of hydroxyprogesterone caproate, of between 250 to 500 mg depending on week of gestation (Shearman 1963).

The two studies that used either oral or IM routes of administration, but did not report the results for the women separately (Berle 1980; Tognoni 1980), used 15 to 20 mg/day orally of allylestrenol or 250 mg IM of hydroxyprogesterone caproate daily or every other day, and 10 mg/day orally of allylestrenol or 25 mg IM every five days of hydroxyprogesterone caproate respectively.

The remaining three studies (Gerhard 1987; Nyboe Anderson 2002; Swyer 1953) delivered treatment via 25 mg twice daily progesterone suppositories, 200 mg three times daily progesterone suppositories and six times 25 mg progesterone pellets inserted within the gluteal muscle, respectively.

Duration of treatment

There was a wide variation in treatment duration between studies. One study continued treatment until miscarriage or until 14 days after the resolution of symptoms (Gerhard 1987); two studies continued treatment for 14 or 17 days (Corrado 2002; Moller 1965); one study continued treatment for 21 days (Nyboe Anderson 2002); one study continued treatment for five weeks (Reijnders 1988); one study continued treatment for eight weeks (Tognoni 1980); one study continued treatment until the 24th week of pregnancy (Shearman 1963); and one study continued treatment until miscarriage or until 36 weeks' gestation (Le Vine 1964). One study continued treatment until the 12th week of gestation (El-Zibdeh 2005). In the remaining five studies treatment duration was either not stated or unclear (Berle 1980; Goldzieher 1964; Klopper 1965; MacDonald 1972; Swyer 1953).

Placebo/control

Ten of the included studies compared treatment with placebo (Berle 1980; Gerhard 1987; Goldzieher 1964; Klopper 1965; Le Vine 1964; MacDonald 1972; Moller 1965; Reijnders 1988; Shearman 1963; Tognoni 1980). The remaining four studies compared progestogen administration with no treatment (Corrado 2002; El-Zibdeh 2005; Nyboe Anderson 2002; Swyer 1953).

Baseline characteristics of participants

Gravida and parity

Two studies required women to have had three or more consecutive miscarriages (El-Zibdeh 2005; Le Vine 1964), and five trials required women to have suffered two or more consecutive miscarriages (Goldzieher 1964; Klopper 1965; MacDonald 1972;

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shearman 1963; Swyer 1953). In addition, one study (MacDonald 1972) required women to have cervical mucus ferning as evidence of "significant hormonal imbalance". Five trials accepted women with threatened imminent pregnancy loss, whether or not they had a history of previous pregnancy loss (Berle 1980; Gerhard 1987; Moller 1965; Reijnders 1988; Tognoni 1980). The remaining two studies (Corrado 2002; Nyboe Anderson 2002) enrolled women who had had amniocentesis and in vitro fertilization respectively, regardless of obstetric history.

Only one study excluded women who had experienced a live birth (Klopper 1965).

Gestation

Nine studies only accepted women within the first trimester of pregnancy (El-Zibdeh 2005; Gerhard 1987; Klopper 1965; MacDonald 1972; Nyboe Anderson 2002; Reijnders 1988; Shearman 1963; Swyer 1953; Tognoni 1980), while three studies accepted women to the 20th gestational week (Berle 1980; Corrado 2002; Le Vine 1964). It was unclear in the remaining studies what gestational cut off, if any, was used (Goldzieher 1964; Moller 1965).

Studied outcomes

- Miscarriage: all 14 studies included miscarriage as an outcome.
- Preterm birth: seven studies reported preterm delivery (Corrado 2002; El-Zibdeh 2005; Gerhard 1987; Goldzieher 1964; Le Vine 1964; Reijnders 1988; Swyer 1953).
- Intrauterine fetal death/still birth: two studies reported intrauterine fetal death/still birth as an outcome (Corrado 2002; Swyer 1953).
- Fetal genital abnormalities/teratogenic effects, fetal deformities: five studies (Moller 1965; El-Zibdeh 2005; Gerhard 1987; Le Vine 1964; Reijnders 1988) reported fetal or genital abnormalities, or both, as an outcome.
- Neonatal death: one study reported a neonatal death (Swyer 1953) and one reported perinatal death (El-Zibdeh 2005).
- Low birthweight less than 2500 g: birthweight was reported as an outcome in three studies (Corrado 2002; Gerhard 1987; Nyboe Anderson 2002). However, only Gerhard 1987 reported individual birthweights. Corrado 2002 and Nyboe Anderson 2002 only published a mean range.
- Severity of morning sickness, intensified headache, nausea, or breast tenderness: no trials reported on these as separate outcomes. However, general side effects experienced by the mother were reported in two studies (Le Vine 1964; Moller 1965).
- Thromboembolic events: no trials reported thromboembolic rates as an outcome.
- Admission to special care unit: no trials reported admission to special care units as an outcome.
- Maternal depression: no trials reported maternal depression as an outcome.
- Subsequent fertility: no trials reported subsequent fertility as an outcome.

Support/sponsorship

Four studies reported support or sponsorship from pharmaceutical companies (Goldzieher 1964; MacDonald 1972; Moller 1965; Shearman 1963).

Excluded studies

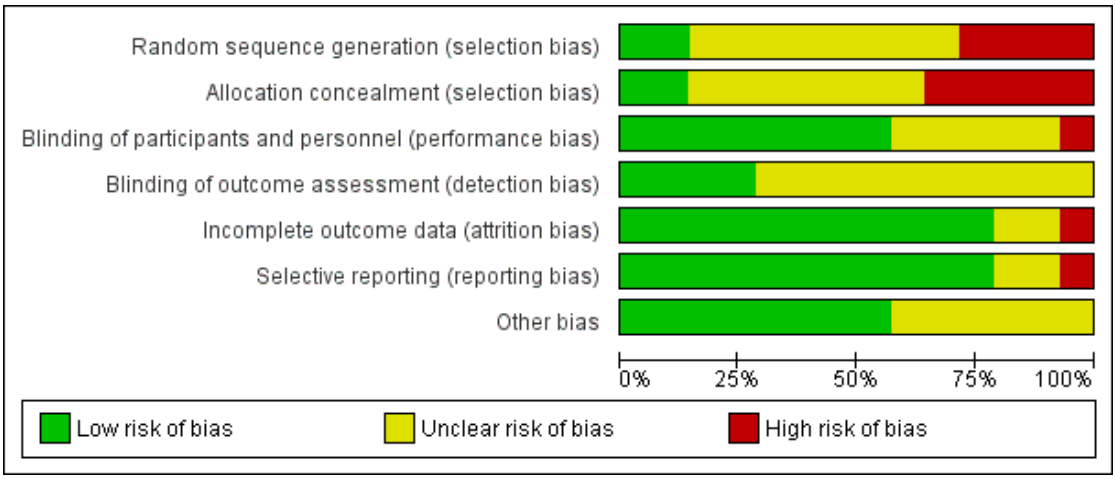
On obtaining the full papers, five papers were found not to be randomized controlled trials (Check 1985; Check 1987a; Daya 1988; Rock 1985; Sidelnikova 1990), and it was unclear if there was any randomization in another (Check 1987b). Five studies had outcomes that were irrelevant to the current review (Brenner 1962; Johnson 1975; Kyrou 2011; Sondergaard 1985; Turner 1966), three used progestogen combination therapy rather than progestogen alone (Check 1995; Prietl 1992; Shu 2002), one did not administer progestogen during pregnancy (Clifford 1996), and one compared two types of progestogen rather than progestogen with no treatment or a placebo group (Smitz 1992). One additional trial was excluded due to being terminated before data collection was complete (Fuchs 1966). For the update, one trial was excluded due to using progestogen therapy after 20 weeks' gestation to prevent preterm labour (Norman 2006).

Risk of bias in included studies

See Figure 2; Figure 3 for a summary of risk of bias in included studies.

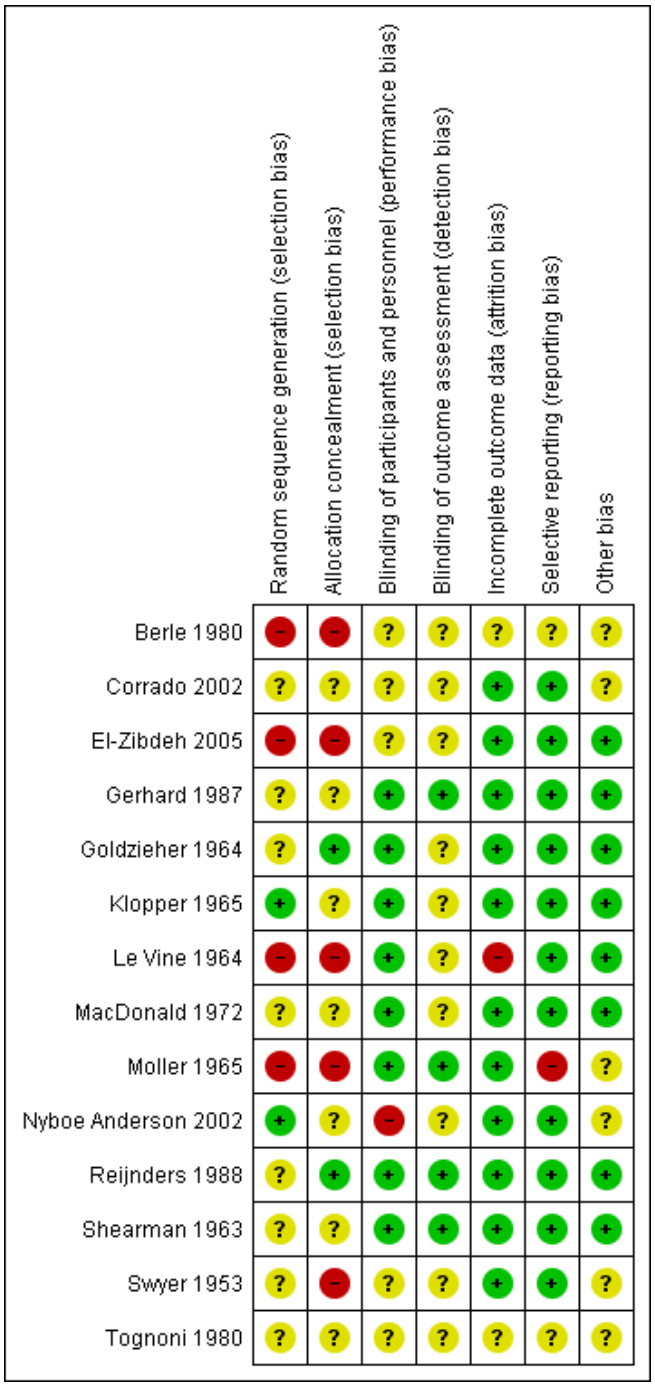
Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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



Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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



Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Allocation

Of the 14 studies that met the inclusion criteria, one used a random table produced by a statistician (Klopper 1965); one used a computer-generated randomization list using clusters of 10 (Nyboe Anderson 2002); two used alternation (Berle 1980; Le Vine 1964); one allocated women by odd and even admission number (Moller 1965); one randomized by day of the week (El-Zibdeh 2005); while the randomization of seven studies was unclear from the papers (Corrado 2002; Gerhard 1987; Goldzieher 1964; MacDonald 1972; Reijnders 1988; Shearman 1963; Tognoni 1980). In the final study (Swyer 1953), two centers took part. One center allocated by alternation, while the paper states that the other used "randomization". However, the method of randomization is not stated.

Of the 14 studies that met the inclusion criteria, three studies used ampules or bottles coded 'A' or 'B' by an unknown source (Goldzieher 1964; Le Vine 1964; Shearman 1963

One study displayed adequate allocation concealment, using sequentially numbered ampules provided by the pharmaceutical company (Reijnders 1988); in one study sequentially numbered bottles were used and the code was not broken until end (Goldzieher 1964); in five studies allocation concealment was clearly inadequate (Berle 1980; El-Zibdeh 2005; Le Vine 1964; Moller 1965; Swyer 1953); while the allocation in the remaining studies was unclear (Corrado 2002; Gerhard 1987; Klopper 1965 MacDonald 1972; Nyboe Anderson 2002; Shearman 1963; Tognoni 1980).

Blinding

Participants and providers were blinded in some studies but the majority of trials did not report on blinding of participants, providers, or outcome assessors. Eight studies used double blinding (where both the participant and treating provider do not know the allocation) (Gerhard 1987; Goldzieher 1964; Klopper 1965; Le Vine 1964; MacDonald 1972; Moller 1965; Reijnders 1988; Shearman 1963). It was unclear whether any blinding was used in the remaining included studies (Berle 1980; Corrado 2002; El-Zibdeh 2005; Swyer 1953; Tognoni 1980). In one study, the participants knew whether they were stopping the medication or not and the providers likely knew as well (Nyboe Anderson 2002).

Incomplete outcome data

Most studies had low rates of attrition and accounted for participants well.

Of the three studies that reported withdrawals or exclusions (Corrado 2002; Gerhard 1987; Tognoni 1980), no study performed an intention-to-treat analysis.

One study reported a large number of dropouts (Le Vine 1964). Fifty-six women were randomized but 26 women were excluded from the analysis: 16, who after randomization, were found not to be pregnant; and 10 who failed to return for injections.

Selective reporting

The majority of studies reported on all planned outcomes relevant to this review.

Other potential sources of bias

Power calculation

Three studies documented power calculations. One study (Gerhard 1987) calculated that to have a "95% confidence limit," 64 women had to be randomized. The trialists successfully enrolled 64 participants but suffered eight dropouts. The second study (Reijnders 1988) calculated that to have 80% power, 80 women needed to be enrolled. Only 64 were enrolled. The final study (Nyboe Anderson 2002) calculated that to have 80% power with a 95% confidence interval, 300 women had to be enrolled. They successfully enrolled 303.

Number of centers

One study had 12 participating centers (Tognoni 1980), one had two main participating centers with additional participating physicians (Goldzieher 1964), four had two participating centers (Klopper 1965; Nyboe Anderson 2002; Shearman 1963; Swyer 1953), five were single center (Berle 1980; Corrado 2002; El-Zibdeh 2005; Gerhard 1987; Moller 1965), and in two studies the number of participating centers was not stated (Le Vine 1964; Reijnders 1988).

See Characteristics of included studies tables for individual details.

Effects of interventions

Fourteen trials (2158 women) met the inclusion criteria.

Progestogen versus placebo/no treatment

Primary outcomes

Miscarriage

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

The meta-analysis of the 14 included studies (2158 women) showed no statistically significant difference in miscarriage rates between progestogen and placebo groups (Peto odds ratio (Peto OR) 0.99; 95% confidence interval (CI) 0.78 to 1.24), Analysis 1.1.

A sensitivity analysis eliminating the studies at high risk of bias (Berle 1980; El-Zibdeh 2005; Le Vine 1964; Moller 1965; Swyer 1953) did not change the results of the analysis (Peto OR 1.03, 95% CI 0.71 to 1.49).

A subgroup analysis was performed comparing studies that did use a placebo control and those that did not use a placebo (Corrado 2002; El-Zibdeh 2005; Nyboe Anderson 2002; Swyer 1953). No statistically significant difference in miscarriage rates between the progestogen and placebo group was demonstrated (Peto OR 1.15; 95% CI 0.88 to 1.50), Analysis 1.2.

The statistical interaction test suggests that there is a difference in treatment effect between subgroups (Test for subgroup differences: Chi² = 4.58, df = 1 (P = 0.03), I² = 78.2%), Analysis 1.2.

Women with a history of three or more consecutive miscarriages

Two trials enrolled only women who had suffered three or more consecutive miscarriages (El-Zibdeh 2005; Le Vine 1964). Two others provided separate pregnancy outcome data by number of previous consecutive pregnancy losses (Goldzieher 1964; Swyer 1953). The meta-analysis showed a statistically significant reduction in miscarriage in favor of those randomized to the progestogen group (Peto OR 0.39; 95% CI 0.21 to 0.72), Analysis 1.3. However as these trials were of poorer methodological quality and might be prone to selection bias, these findings should be interpreted with caution. Because of a clinical trend toward evaluating women with 2 prior miscarriages for causes, the subgroup analysis also analyzed women with at least 2 prior miscarriages. There was a trend but not a significant reduction in miscarriage rates after progestogen treatment in this group (Peto OR 0.68; 95% CI 0.43 to 1.07).Analysis 1.3.

The statistical interaction test suggests that there is a difference in treatment effect between subgroups (Test for subgroup differences: Chi² = 10.73, df = 2 (P = 0.005), I² = 81.4%), Analysis 1.3.

Route of administration of progestogen

Five studies compared oral progestogen with placebo/no treatment (El-Zibdeh 2005; Goldzieher 1964; Klopper 1965; Moller 1965; MacDonald 1972). The meta-analysis showed no statistically significant difference in miscarriages between the progestogen and placebo group (Peto OR 0.96; 95% CI 0.65 to 1.40), Analysis 1.4.

Four studies compared intramuscular progestogen with placebo/no treatment (Corrado 2002; Le Vine 1964; Reijnders 1988; Shearman 1963). The meta-analysis showed no statistically significant difference in miscarriages between the progestogen and placebo group (Peto OR 0.77; 95% CI 0.36 to 1.68), Analysis 1.4

One study compared vaginally administered progestogen with placebo/no treatment (Gerhard 1987), with a second comparing it to no treatment (Nyboe Anderson 2002). The meta-analysis showed no statistically significant difference between the two groups with respect to the incidence of recurrent miscarriage (Peto OR 0.74; 95% CI 0.40 to 1.35), Analysis 1.4.

The statistical interaction test suggests that there is no difference in treatment effect between subgroups (Test for subgroup differences: Chi² = 0.62, df = 2 (P = 0.73), I² = 0%), Analysis 1.4.

Secondary outcomes

Preterm birth

Seven studies reported an incidence of premature birth (Corrado 2002; El-Zibdeh 2005; Gerhard 1987; Goldzieher 1964; Le Vine 1964; Reijnders 1988; Swyer 1953). The meta-analysis showed no statistically significant difference in preterm births between the progestogen and placebo group (Peto OR 1.10; 95% CI 0.67 to 1.81), Analysis 1.5. In addition, the three arms of Moller et al (Moller 1965) reported 18 preterm births but failed to give data on how these were divided between the progestogen and placebo groups.

Neonatal death

Five studies gave neonatal death as an outcome. One study reported no neonatal deaths in either group (Gerhard 1987); one study reported no difference in perinatal death (2.8% in progesterone group, 2.9% in controls) (El-Zibdeh 2005); the meta-analysis of the five studies (El-Zibdeh 2005; Gerhard 1987; Reijnders 1988; Swyer 1953; Tognoni 1980 showed no significant difference between treatment and placebo (Peto OR 1.38; 95% CI 0.72 to 2.64), Analysis 1.6. In addition, Moller 1965 reported eight neonatal deaths but again failed to give data on how these were divided between the progestogen and placebo groups.

Birthweight

One study (Gerhard 1987) studied birthweight. It reported no incidence of a baby born weighing less than 2500 g. Two other studies also reported birthweight but provided a mean range rather than individual data (Corrado 2002; Nyboe Anderson 2002). There were no statistically significant differences in the mean weight of babies in either study.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Fetal abnormalities

Four studies reported fetal abnormalities as an outcome (El-Zibdeh 2005; Gerhard 1987; Le Vine 1964; Reijnders 1988). Two studies reported no incidence of fetal abnormalities (Gerhard 1987; Le Vine 1964). One study reported a single case of fetal genital abnormality in the progestogen group (Reijnders 1988). There was no statistically significant difference in fetal genital anomalies (Peto OR 7.64; 95% CI 0.15 to 385.21), Analysis 1.7. One study reported two anomalies in the progestogen group (neural tube defect and non-immune hydrops) and one case of multiple anomalies in the control group in a baby with Down's syndrome (El-Zibdeh 2005). No genital anomalies were noted in that study. In addition, the Moller et al study (Moller 1965) reported one case of fetal abnormality in the progestogen group but, due to inconsistency in the method used for reporting numbers, could not be included in the meta-analysis. (That is, in total there were 131 successful pregnancies and 139 live births. The numbers for successful pregnancies are divided into progestogen and placebo groups. However, the live births are not separated in this manner. The one baby with fetal abnormalities is given in the figures for live births rather than successful pregnancies).

Maternal adverse events

Two studies listed maternal adverse effects as outcomes (Le Vine 1964; Moller 1965). No events were noted.

DISCUSSION

Summary of main results

The aim of this review was to assess the effectiveness of progestogens to prevent miscarriage. Although there has been much speculation that progestogens may reduce the miscarriage rate, the results of this meta-analysis show no statistically significant difference between women receiving progestogen and those receiving only placebo or no treatment, when no provision is made for obstetric history. Subgroup analysis by method of administration (oral, intramuscular or vaginal) also showed no statistically significant difference between progestogen and placebo groups.

However, when provision was made for obstetric history, by way of a subgroup analysis only including women who had suffered three or more consecutive miscarriages directly prior to the studied pregnancy, a statistically significant difference was found in favor of the progestogen group. This finding should be approached with caution, however, as numbers are small and the trials were of poor methodological quality. Two trials are currently underway to further evaluate therapy in this subgroup of women. In addition, some studies included data for women who had two or more miscarriages but as this is not the classic definition of recurrent miscarriage, a separate analysis including these women was not carried out.

The meta-analysis showed no statistically significant difference in the number of fetal abnormalities (including virilization and hypospadias) in babies whose mothers had been given progestogens whilst in vitro, nor in intrauterine death/still birth or neonatal death.

There has been much discussion as to whether progestogen may prevent preterm birth (Keirse 1990). There was no statistically significant difference in our meta-analysis between the number of preterm births in the progestogen and placebo groups. However, it is important to note that this systematic review only assesses progestogen given in early pregnancy to prevent miscarriage, rather than trials assessing progestogen given in the second or third trimester to try to prevent preterm delivery.

No studies reported adverse maternal effects.

Overall completeness and applicability of evidence

The data appear mostly consistent, particularly regarding women with recurrent losses. The ongoing trials in this population will provide data for future updates.

Quality of the evidence

Overall, the quality of the evidence was moderately good. The majority of the studies were conducted before robust reporting of methods was instituted. This led to "unclear" evaluations for many of the study 'Risk of bias' categories based simply on the area not being explicitly stated. For the time the studies were performed, the overall quality appears to be reasonable.

Potential biases in the review process

The review process identified trials from a heterogenous set of conditions. All used the same treatment for the same outcome, however the differences in condition make the data difficult to interpret.

Agreements and disagreements with other studies or reviews

These results for women with recurrent miscarriage agree with a systematic review conducted by Coomarasamy 2011 that included four of the trials included in this review.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the routine use of progestogen to prevent miscarriage in early to mid-pregnancy.

Implications for research

A finding of a significantly reduced miscarriage rate in women with a history of recurrent miscarriage (three or more consecutive miscarriages) deserves further study.

ACKNOWLEDGEMENTS

The review authors would like to thank Lynn Hampson for her search of the Cochrane Pregnancy and Childbirth Group's Trials Register.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pregnancy and Childbirth Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Berle 1980 ***{published data only}***
Berle P, Budenz M, Michaelis J. Is hormonal therapy still justified in imminent abortion?. *Zeitschrift fur Geburtshilfe und Perinatologie* 1980;**184**:353–8.

Corrado 2002 ***{published data only}***
Corrado F, Dugo C, Cannata M, Di Bartolo M, Scilipoti A, Stella N. A randomised trial of progesterone prophylaxis after midtrimester amniocentesis. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2002;**100** (2):196–8.

El-Zibdeh 2005 ***{published data only}***
El Zibdeh M. Randomized clinical trial comparing the efficacy of dydrogesterone and human chorionic gonadotropin. *Climacteric* 2002;**5**(Suppl 1):136.
El Zibdeh M. Randomized study comparing the efficacy of reducing spontaneous abortion following treatment with progesterone and human chorionic gonadotropin (hCG). *Fertility and Sterility* 1998;**70**(3 Suppl 1):S77–S78.
* El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. *Journal of Steroid Biochemistry & Molecular Biology* 2005;**97**(5):431–4.

Gerhard 1987 ***{published data only}***
Gerhard I, Gwinner B, Eggert-Kruse W, Runnebaum B. Double-blind controlled trial of progesterone substitution in threatened abortion. *Biological Research in Pregnancy and Perinatology* 1987;**8**:26–34.

Goldzieher 1964 ***{published data only}***
Goldzieher JW. Double-blind trial of a progestin in habitual abortion. *JAMA* 1964;**188**(7):651–4.

Klopper 1965 ***{published data only}***
Klopper A, MacNaughton M. Hormones in recurrent abortion. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1965;**72**:1022–8.

Le Vine 1964 ***{published data only}***
Le Vine L. Habitual abortion. A controlled clinical study of progestational therapy. *Western Journal of Surgery* 1964;**72**: 30–6.

MacDonald 1972 ***{published data only}***
MacDonald RR, Goulden R, Oakey RE. Cervical mucus, vaginal cytology and steroid excretion in recurrent abortion. *Obstetrics & Gynecology* 1972;**40**(3):394–402.

Moller 1965 ***{published data only}***
Moller K, Fuchs F. Double blind controlled trial of 6-methyl-17-acetoxyprogesterone in threatened abortion. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1965;**72**:1042–4.

Nyboe Anderson 2002 ***{published data only}***
Nyboe Anderson A, Popovic-Todorovic B, Schmidt K, Loft A, Lindhard A, Hojgaard A, et al. Progesterone supplement during early gestations after IVF or ICSI has no effect on the delivery rates: a randomized controlled trial. *Human Reproduction* 2002;**17**(2):357–61.

Reijnders 1988 ***{published data only}***
Reijnders FJL, Thomas CMG, Doesburg WH, Rolland R, Eskes TKAB. Endocrine effects of 17 alpha-hydroxyprogesterone caproate during early pregnancy: a double-blind clinical trial. *British Journal of Obstetrics and Gynaecology* 1988;**95**:462–8.

Shearman 1963 ***{published data only}***
Shearman R, Garrett W. Double-blind study of effect of 17-hydroxyprogesterone caproate on abortion rate. *British Medical Journal* 1963;**1**:292–5.

Swyer 1953 ***{published data only}***
Swyer GIM, Daley D. Progesterone implantation in habitual abortion. *British Medical Journal* 1953;**1**:1073–86.

Tognoni 1980 ***{published data only}***
Tognoni G, Ferrario L, Inzalaco M, Crosignani P. Progestogens in threatened abortion. *Lancet* 1980;**2**(8206): 1242–3.

References to studies excluded from this review

Brenner 1962 ***{published data only}***
Brenner W, Hendricks C. Effect of medroxyprogesterone acetate upon the duration and characteristics of human gestation labour. *American Journal of Obstetrics and Gynecology* 1962;**83**(8):1094–8.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Check 1985 *{published data only}*
Check J, Wu C-H, Adelson H. Decreased abortion in HMG-induced pregnancies. *International Journal of Fertility* 1985;**30**(3):45–7.

Check 1987a *{published data only}*
Check J, Chase J, Nowroozi K, Wu C, Adelson H. Progesterone therapy to decrease first-trimester spontaneous abortions in previous aborters. *International Journal of Fertility* 1987;**32**(3):192–9.

Check 1987b *{published data only}*
Check J, Chase J, Wu C, Adelson H, Teichman M, Rankin A. The efficacy of progesterone in achieving successful pregnancy: prophylactic use during luteal phase in anovulatory women. *International Journal of Fertility* 1987; **32**(2):135–8.

Check 1995 *{published data only}*
Check JH, Tarquini P, Gandy P, Lauer C. A randomized study comparing the efficacy of reducing the spontaneous abortion rate following lymphocyte immunotherapy and progesterone treatment vs progesterone alone in primary habitual aborters. *Gynecologic and Obstetric Investigation* 1995;**39**:257–61.

Clifford 1996 *{published data only}*
Clifford K, Rai R, Watson H, Franks S, Regan L. Does suppressing luteinising hormone secretion reduce the miscarriage rate? Results of a randomised controlled trial. *BMJ* 1996;**312**:1508–11.

Daya 1988 *{published data only}*
Daya S, Ward S, Burrows E. Progesterone profiles in luteal phase defect cycles and outcome of progesteron treatment in patients with recurrent spontaneous abortion. *American Journal of Obstetrics and Gynecology* 1988;**158**(2):225–32.

Fuchs 1966 *{published data only}*
Fuchs F, Olsen P. An attempted double-blind controlled trial of progesterone therapy in habitual abortion. *Ugeskrift for Laeger* 1966;**128**:1461–2.

Johnson 1975 *{published data only}*
Johnson J, Austin K, Jones G, Davis G, King T. Efficacy of 17 alpha-hydroxyprogesterone caproate on the prevention of premature labour. *New England Journal of Medicine* 1975;**298**(14):675–80.

Kyrou 2011 *{published data only}*
Kyrou D, Fatemi HM, Zepiridis L, Riva A, Papanikolaou EG, Tarlatzis BC, et al. Does cessation of progesterone supplementation during early pregnancy in patients treated with recFSH/GnRH antagonist affect ongoing pregnancy rates? A randomized controlled trial. *Human Reproduction* 2011;**26**(5):1020–4.

Norman 2006 *{published data only}*
Norman JE. Double blind randomised placebo controlled study of progesterone for the prevention of preterm birth in twins (STOPPIT). National Research Register. www.nrr.nhs.uk (accessed 6 July 2006).

Prietl 1992 *{published data only}*
Prietl G, Diedrich K, Van der Ven HH, Luckhaus J, Krebs D. The effect of 17alpha-hydroxyprogesterone caproate/ oestradiol valerate on the development and outcome of early pregnancies following in vitro fertilization and embryo transfer: a prospective and randomized controlled trial. *Human Reproduction* 1992;**7**(1):1–5.

Rock 1985 *{published data only}*
Rock J, Colston Wentz A, Cole K, Kimball A, Zacur H, Early S, et al. Fetal malformations following progesterone therapy during pregnancy: a preliminary report. *Fertility and Sterility* 1985;**44**(1):17–9.

Shu 2002 *{published data only}*
Shu J, Miao P, Wang RJ. Clinical observation on effect of Chinese herbal medicine plus human chorionic gonadotropin and progesterone in treating anticardiolipin antibody-positive early recurrent spontaneous abortion. *Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi/Chinese Journal of Integrated Traditional and Western Medicine* 2002;**22**(6):414–6.

Sidelnikova 1990 *{published data only}*
Sidelnikova VM, Demidova EM, Borisova IF, Dondukova TM, Absava GI, Korkhov VV. The use of acetomepegrenol in the therapy of threatened abortion. *Akusherstvo i Ginekologiia* 1990;**66**(9):37–40.

Smitz 1992 *{published data only}*
Smitz J, Devroey P, Faguer B, Bourgain C, Camus M, Van Steirteghem AC. Randomized prospective trial comparing supplementation of the luteal phase and of early pregnancy by natural progesterone given by intramuscular or vaginal administration. *Revue Francaise de Gynecologie et d Obstetrique* 1992;**87**:507–16.

Sondergaard 1985 *{published data only}*
Sondergaard F, Ottesen B, Detlefsen GU, Schierup L, Pederson SC, Lebech PE. Progesterone treatment of cases of threatened pre-term delivery in women with a low level of plasma progesterone. *Contraception, Fertilite, Sexualite* 1985;**13**(12):1227–31.

Turner 1966 *{published data only}*
Turner SJ, Mizock GB, Feldman GL. Prolonged gynecologic and endocrine manifestations subsequent to administration of medroxyprogesterone acetate during pregnancy. *American Journal of Obstetrics and Gynecology* 1966;**95**:222–7.

References to ongoing studies

Coomarasamy 2012 *{published data only}*
Coomarasamy A. First trimester progesterone therapy in women with a history of unexplained recurrent miscarriages: a randomised double-blind placebo-controlled multi-centre trial (The PROMISE [PROgesterone in recurrent MIScarriagE] Trial). http://www.controlled-trials.com/ ISRCTN92644181 (accessed 11.01.2012).

Raddatz 2006 *{published data only}*
Raddatz G. Habitual abortion study: oral dydrogesterone treatment during pregnancy in women with recurrent miscarriage. http://clinicaltrials.gov/ct2/show/ NCT00193674 (accessed 21 March 2006).

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Walch 2005 *{published data only}*

Walch K, Hefler L, Nagele F. Oral dydrogesterone treatment during the first trimester of pregnancy: the prevention of miscarriage study (PROMIS). A double-blind, prospectively randomized, placebo-controlled, parallel group trial. *Journal of Maternal-Fetal & Neonatal Medicine* 2005;**18**(4):265–9.

Additional references

Alfirevic 2012

Alfirevic Z, Stampalija T, Roberts D, Jorgensen AL. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD008991.pub2]

Atkin 1998

Atkin LC, Arcelus M, Fernandez A, Tolbert K. *La Psicologia en el Ambito Perinatal*. Mexico D.F: INPER, 1988.

Bamigboye 2003

Bamigboye AA, Morris J. Oestrogen supplementation, mainly diethylstilbestrol, for preventing miscarriages and other adverse pregnancy outcomes. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: 10.1002/14651858.CD004353]

Briggs 2011

Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 9th Edition. Philadelphia: Lippincott Williams & Wilkins, 2011.

Burgoyne 1991

Burgoyne PS, Holland K, Stephens R. Incidence of numerical chromosome anomalies in human pregnancy estimation from induced and spontaneous abortion data. *Human Reproduction* 1991;**6**(4):555–65.

Coomarasamy 2011

Coomarasamy A, Truchanowicz EG, Rai R. Does first trimester progesterone prophylaxis increase the live birth rate in women with unexplained recurrent miscarriages?. *BMJ* 2011;**342**:d1914.

Coulam 1991

Coulam CB. Epidemiology of recurrent spontaneous abortion. *American Journal of Reproductive Immunology* 1991;**26**:23–7.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor(s). *Systematic Reviews in Health Care: Meta-analysis in Context*. London: BMJ Books, 2001.

Dyregrove 1987

Dyregrove A, Mathieson SB. Stillbirth, neonatal death and SIDS: parental reactions. *Scandanavian Journal of Psychology* 1987;**28**:104–14.

Goldstein 1989

Goldstein P, Berrier J, Rosen S, Sacks HS, Chalmers TC. A meta-analysis of randomised control trials of progestational agents in pregnancy. *British Journal of Obstetrics and Gynaecology* 1989;**96**:265–74.

Grudzinskas 1995

Grudzinskas JG. Endocrinocolgical and metabolical assesssment of early pregnancy. In: Chamberlain G editor (s). *Tumbull's Obstetrics*. London: Pearson Professional Ltd, 1995.

Higgins 2005

Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.4 [updated March 2005]. In: The Cochrane Library, Issue 2, 2005. Chichester, UK: John Wiley & Sons, Ltd.

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.

Howie 1995

Howie PG. Abortion and ectopic pregnancy. In: Whitfield CR editor(s). *Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates*. Oxford: Blackwell Science Ltd, 1995.

Karamadian 1992

Karamadian LM, Grimes DA. Luteal phase deficiency. Effect of treatment on pregnancy rates. *American Journal of Obstetrics and Gynecology* 1992;**167**:1391–8.

Keirse 1990

Keirse M J. Progestogen administration in pregnancy may prevent preterm delivery. *British Journal of Obstetrics and Gynaecology* 1990;**97**(2):149–54.

Lede 2005

Lede R, Duley L. Uterine muscle relaxant drugs for threatened miscarriage. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD002857.pub2]

McBride 1991

McBride WZ. Spontaneous abortion. *American Family Physician* 1991;**43**:175–82.

Morley 2013

Morley LC, Simpson N, Tang T. Human chorionic gonadotrophin (hCG) for preventing miscarriage. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD008611.pub2]

Neilson 2006

Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD002253.pub3]

Porter 2006

Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD000112.pub2]

Regan 1989

Regan L, Braude PB, Trembath PR. Influences of past reproductive performance on risk of spontaneous abortion. *BMJ* 1989;**299**:541–5.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

RevMan 2003 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

RevMan 2012 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Royal 2001
Royal College of Obstetricians and Gynaecologists. The management of recurrent miscarriage. http://www.rcog.org.uk/guidelines/recurrent.html (accessed 2001).

Rumbold 2011
Rumbold A, Middleton P, Pan N, Crowther CA. Vitamin supplementation for preventing miscarriage. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: 10.1002/14651858.CD004073.pub3]

Simpson 1991
Simpson JL. Fetal wastage. In: Gabe SG, Simpson JL editor (s). *Obstetrics. Normal and Problem Pregnancies*. New York: Churchill Livingstone Inc, 1991.

Szabo 1996
Szabo I, Szilagyi A. Management of threatened abortion. *Early Pregnancy* 1996;**2**(4):233–40.

Vance 1991
Vance JC, Foster WJ, Najman JM, Embelton, Thearle MJ, Hogden FM. Early parental responses to sudden infant death, stillbirth or neonatal death. *Medical Journal of Australia* 1991;**155**(5):292–7.

Woods 1987
Woods JR, Esposito JL. *Pregnancy Loss: Medical Therapeutics and Practical Considerations*. Baltimore: Williams and Wilkins, 1987.

References to other published versions of this review

Haas 2008
Haas DM, Ramsey PS. Progestogen for preventing miscarriage. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD003511.pub2]

Oates-Whitehead 2003
Oates-Whitehead RM, Haas DM, Carrier JAK. Progestogen for preventing miscarriage. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003511]

* *Indicates the major publication for the study*

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CHARACTERISTICS OF STUDIES

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

Berle 1980

Methods	Unit of randomization: pregnancy. Method of randomization: alternation. Timing of randomization: up to the 20th week of gestation. Blinding: no. Power calculation: nil. Number of centers: 1. 300 women randomized, 0 exclusions, 300 women analyzed. Source of funding: not stated.
Participants	Women up to 20 weeks' gestation presenting with bleeding. Age: 12% less than 21, 61% between 21 and 30, 17% between 31 and 35, and 9% older than 35 Location: Germany. Timing and duration: 1976-1978.
Interventions	90% of the treatment group received allylestrenol (15 mg-20 mg orally per day) 10% received 250 mg of hydroxyprogesterone caproate intramuscularly every day or every 2 days Placebo: yes. Duration: not stated.
Outcomes	Miscarriage.
Notes	Language of publication: German.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomized.
Allocation concealment (selection bias)	High risk	Alternating treatments.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Berle 1980 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Unclear risk	Unknown.

Corrado 2002

Methods	Unit of randomization: pregnancy. Method of randomization: unknown. Timing of randomization: at amniocentesis (mid-second trimester). Blinding: unclear. Power calculation: no. Number of centers: 1. 616 women randomized, 32 exclusions, 584 women analyzed. Source of funding: not stated.
Participants	Women undergoing mid-second trimester amniocentesis. Age: 36.4 +/- 3.6 in the progestogen group and 36.5 +/- 4.7 in the control group Location: Italy. Timing and duration: 1997 to 1999.
Interventions	200 mg/day IM of natural progesterone for 3 days following amniocentesis, followed by 340 mg IM hydroxyprogesterone caproate twice a week until completion of the second week from the time of amniocentesis Placebo: no. Control group received no treatment.
Outcomes	Miscarriage. Preterm delivery. Birthweight.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Corrado 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported all outcomes.
Selective reporting (reporting bias)	Low risk	Reported all outcomes.
Other bias	Unclear risk	Unclear from methods.

El-Zibdeh 2005

Methods	Unit of randomization: pregnancy. Method of randomization: day of week attending clinic. Timing of randomization: presentation for new pregnancy. Blinding: unclear. Power calculation: no. Number of centers: 1. 180 women randomized, 0 exclusions, 180 women analyzed. Source of funding: not stated.
Participants	Women (< 35 years old) with at least 3 consecutive unexplained abortions with same husband with a new pregnancy Age: treatment 22% age 20-24 years, 36% age 25-29 years, 41.5% age 30-34 year, control: 21% age 20-24 years, 48% age 25-29 years, 31% age 30-34 years Location: Jordan. Timing and duration: 1994-2000.
Interventions	10mg BiD oral dydrogesterone, 5000 IU IM hCG every 4 days, or no treatment Placebo: no, control group had no treatment. Duration: until miscarriage or 12th gestational week.
Outcomes	Miscarriage, preterm delivery, fetal malformations, perinatal death (not analyzed in review: hospitalization for vaginal bleeding)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Allocation by day of the week.
Allocation concealment (selection bias)	High risk	Allocation by day of the week.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

El-Zibdeh 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Does not appear to be incomplete data.
Selective reporting (reporting bias)	Low risk	None noted.
Other bias	Low risk	None noted.

Gerhard 1987

Methods	Unit of randomization: pregnancy. Method of randomization: unclear. Timing of randomization: before the 13th week of gestation. Blinding: yes (double). Power calculation: yes (95% of 32 women were randomized to each group). Number of centers: 1. 64 women randomized. 8 women excluded. 56 women analyzed. Source of funding: not stated.
Participants	Women with vaginal bleeding in pregnancy and a closed os. Age: treatment mean age - 29.2, placebo mean age 28.7. Location: Germany. Timing and duration: 1983-1984.
Interventions	25 mg BiD progesterone vaginal suppositories. Placebo: yes. Duration: until miscarriage or 14 days from the cessation of symptoms
Outcomes	Miscarriage. Birthweight. Preterm delivery.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gerhard 1987 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"code note broken until completion of the study, so that both staff and patients did not know which of the preparations contained the hormones."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasonable.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None.

Goldzieher 1964

Methods	Unit of randomization: pregnancy. Method of randomization: sequentially-numbered bottles. It is not clear who was responsible for the coding. Timing of randomization: unclear. Blinding: yes (double). Power calculation: nil. Number of centers: 2 main centers. 54 women randomized, 0 women excluded, 54 women analyzed. Source of funding: Upjohn.
Participants	Women who had either: never had a term pregnancy and who had had 2 or more miscarriages or who had had 1 or more term pregnancy followed by a minimum number of 2 consecutive miscarriages All women had to have a urinary pregnanediol of less than 5 mg/day before 8 weeks' gestation and/or less than 7 mg/day by 14 weeks' gestation. Age: not stated. Location: USA.
Interventions	10 mg/day of oral medroxyprogesterone. Placebo: yes. Duration: not stated.
Outcomes	Miscarriage. Preterm delivery.
Notes	
Risk of bias	

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Goldzieher 1964 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Sequentially numbered bottles. Code not broken until end.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Does not appear to be incomplete outcome data.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None apparent.

Klopper 1965

Methods	Unit of randomization: pregnancy. Method of randomization: random schedules generated by a statistician. Timing of randomization: before 10 weeks' gestation. Power calculation: nil. Blinding: yes (double). Number of centers: 2. 33 women randomized, 33 women analyzed. Source of funding: not stated.
Participants	Women who had 2 or more miscarriages, no pregnancy beyond 28 weeks' gestation, were less than 10 weeks into the current pregnancy and with no other obvious causes of miscarriage
Interventions	50 mg BiD of oral cyclopentyl enol ether of progesterone. Placebo: yes. Duration: not stated.
Outcomes	Miscarriage.
Notes	
Risk of bias	

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Klopper 1965 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random schedules generated by statistician.
Allocation concealment (selection bias)	Unclear risk	Given according to a random schedule.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded design - neither patients nor physician knew which of the 2 they were getting
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated but likely blinded also.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None.

Le Vine 1964

Methods	Unit of randomization: pregnancy. Method of randomization: women were alternated between 'Group A' and 'Group B'. It is unclear who decided which group would be treatment and which would be placebo. Timing of randomization: within the 16th week of pregnancy. Power calculation: nil. Blinding: yes (double). Number of centers: not stated. 56 women randomized, 26 women excluded, 30 women analyzed. Source of funding not stated.
Participants	Women who had had 3 consecutive miscarriages, were less than 16 weeks' gestation and with no signs of threatened miscarriage in the current pregnancy Age: 20-42. Location: USA. Timing and duration: unknown.
Interventions	500 mg/week IM of hydroxyprogesterone caproate. Duration: until miscarriage or the 36th week of gestation. Placebo: yes.
Outcomes	Miscarriage. Side effects of treatment suffered by the mother. Deformities in the baby. Preterm birth.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Le Vine 1964 (*Continued*)

Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternating group A and B.
Allocation concealment (selection bias)	High risk	Alternating group A and B.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated double blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	56 women randomized, 26 women excluded, 30 women analyzed.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None.

MacDonald 1972

Methods	Unit of randomization: pregnancy. Method of randomization: unclear. Timing of randomization: after they were found to have evidence of hormonal imbalance on cervical mucus smears. Power calculation: nil. Blinding: yes (double). Number of centers: 1 specialized antenatal center. 40 women randomized, 0 women excluded, 40 women analyzed. Source of funding: grant from N.V. Philips-Duphar.
Participants	Women with 2 or more consecutive proven abortions and then subsequent pregnancy with cervical mucus ferning present
Interventions	2 x 5 mg tablets of dydrogesterone tablets 3 times daily, increased to 4 tablets 3 times daily if ferning persisted, no duration specified Placebo: yes.
Outcomes	Miscarriage.
Notes	

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

MacDonald 1972 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated double blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None.

Moller 1965

Methods	Unit of randomization: pregnancy. Method of randomization: odd and even admission numbers. Timing of randomization: unclear. Power calculation: nil. Blinding: yes (double). Number of centers: 1. 40 women randomized, 0 women excluded, 40 women analyzed. Source of funding: preparations were supplied by Leo Pharmaceuticals
Participants	Women with a positive pregnancy test. Age: not reported. Location: Denmark.
Interventions	20 mg/day of oral medroxyprogesterone for 3 days, followed by 10 mg/day for 11 days. Then from 1961-1962, 40 mg/day of oral medroxyprogesterone for 3 days, followed by 20 mg/day for 11 days Then from 1962-1964, 80 mg/day of oral medroxyprogesterone for 3 days, followed by 40 mg/day for 7 days, followed by 20 mg for 7 days Placebo: yes.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Moller 1965 (*Continued*)

Outcomes	Miscarriage. Side effects of treatment suffered by the mother. Genital abnormalities.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	According to admission numbers - even and odd.
Allocation concealment (selection bias)	High risk	According to admission numbers - even and odd.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded given as "A" and "B" preparations. Code not broken until completion of analysis
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	High risk	Excluded women who aborted within 24 hours of admission.
Other bias	Unclear risk	Dose increased during the 4.5 years of the study. Analyzed in results - likely not a risk of bias

Nyboe Anderson 2002

Methods	Unit of randomization: pregnancy. Method of randomization: computer-generated randomization list. Timing of randomization: when receiving confirmation of a positive pregnancy test. Blinding: unclear. Power calculation: yes (80% power with a 95% CI with 300 women enrolled). Number of centers: 2. 303 women randomized, 0 excluded, 303 women analyzed. Source of funding: not stated.
Participants	Women having undergone IVF or ICSI with a positive pregnancy test 14 days after transfer Age: 32.1 +/- 4.1 in the progestogen group and 32.2 +/- 4.3 in the control group

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Nyboe Anderson 2002 (*Continued*)

	Location: Denmark. Timing and duration: 1999-2000.
Interventions	200 mg TiDs vaginal suppositories. Placebo: no control group received no treatment. Duration: 3 weeks.
Outcomes	Miscarriage. Birthweight.
Notes	After IVF or ICSI.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list in blocks of 10.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants knew whether they were stopping the medication or not and the providers likely knew as well
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Unclear risk	The patient's other physician may have given progesterone later. These data are not included

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Reijnders 1988

Methods	Unit of randomization: pregnancy. Method of randomization: sequentially-coded ampules supplied be the drug company. Timing of randomization: 6-7 weeks' gestation. Blinding: yes (double). Number of centers: not stated. Power calculation: yes (80% with 40 in each group). 64 women randomized, 0 women excluded, 64 women analyzed. Source of funding: Schering.
Participants	Women who fell into 1 or more of the following criteria: pregnancy after ovulation induction; 2 or more previous miscarriages; period of infertility for more than 12 months. Evidence of a viable fetus at 6 weeks of pregnancy was required to be enrolled in the trial Age: not stated. Location: Netherlands. Timing and duration: 2 years. Years not stated.
Interventions	500 mg/week IM of hydroxyprogesterone caproate given IM. Placebo: yes. Duration: from 7 weeks' gestation to 12 weeks' gestation.
Outcomes	Miscarriage. Preterm delivery.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Low risk	Sequentially coded ampules supplied by central location.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically stated but likely blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	None.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Reijnders 1988 (*Continued*)

Other bias	Low risk	None.

Shearman 1963

Methods	Unit of randomization: pregnancy. Method of randomization: unclear. The ampules were said to be coded but who coded these and how women were then allocated to the coded ampules is not stated. Timing of randomization: before the 12th week of gestation. Blinding: yes (double). Power calculation: nil. Number of centers: 2. 50 women randomized. 0 women excluded. 50 women analyzed. Source of funding: preparations supplied by Schering.
Participants	Women having had 2 or more consecutive abortions and who had low or falling pregnanediol levels Exclusions: women with uterine malformations. Age: not stated. Location: London. Duration and timing: not stated.
Interventions	Up to 8 weeks' gestation - 250 ml/week IM hydroxyprogesterone; 8 to 11 weeks' gestation - 375 ml/week IM of 17-a-hydroxyprogesterone; 12 to 16 weeks' gestation - 500 ml/week IM of 17-a-hydroxyprogesterone; 17th to 20th week - 375 mg/week IM of 17-a-hydroxyprogesterone; 21st to 24th week - 250 mg/week IM of 17-a-hydroxyprogesterone Placebo: yes.
Outcomes	Miscarriage.
Notes	Source of funding: preparations supplied by Schering.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Solution A and B - the "correct identity of these substances is not known to any person taking part in this study."

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Shearman 1963 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Low risk	None.

Swyer 1953

Methods	Unit of randomization: pregnancy. Method of randomization of allocation: there were 2 centers in this study. 1 allocated by alternation. It was stated in the paper that the other center used "randomisation". However, method of randomization is not given. Timing of randomization: before 12 weeks' gestation. Blinding: unclear. Power calculation: nil. Number of centers: 2. 113 women were enrolled, 0 women were excluded, 113 women were analyzed Source of funding: not stated.
Participants	Women having had 2 or more consecutive miscarriages before 12 weeks' gestation Exclusions: women with any other known complicating factor (positive Wassermann reaction, extensive cervical tear, uterine malformation, associated medical disease etc) Age: not stated. Location: London. Timing and duration: not stated.
Interventions	6 x 25 mg progesterone pellets inserted within the gluteal muscle either: (a) as soon as pregnancy was confirmed or (b) not later than 10th week of gestation or (c) not later than the earliest previous miscarriage. Placebo: no but had a no-treatment control group. Duration: unclear.
Outcomes	Miscarriage. Preterm delivery. Stillbirth.
Notes	
Risk of bias	

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Swyer 1953 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	High risk	There were 2 centers in this study. 1 allocated by alternation. It was stated in the paper that the other center used "randomisation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None.
Selective reporting (reporting bias)	Low risk	None.
Other bias	Unclear risk	Treatment duration not clearly stated.

Tognoni 1980

Methods	Unit of randomization: pregnancy. Method of randomization: unknown. Timing of randomization: up until the 14th week of gestation. Blinding: unclear. Power calculation: nil. Number of centers: 12. Number of women randomized: 145. Number of exclusions 6. Number of women analyzed: 139. Source of funding: not stated.
Participants	Women with threatened miscarriage up until 14 weeks' gestation Age: not stated. Location: Italy. Timing and duration: not stated.
Interventions	Oral allylestrenol 10 mg/day or 25 mg IM hydroxyprogesterone caproate every 5 days. Placebo: yes. Duration: 8 weeks.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tognoni 1980 (*Continued*)

Outcomes	Miscarriage.	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Only states allocated "at random".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	Unclear risk	Not stated.
Other bias	Unclear risk	Not stated. Brief report in a letter.

BiD: twice daily
CI: confidence interval
hCG: human chorionic gonadotropin
ICSI: intracytoplasmic sperm injection
IM: intramuscular
IU: international unit
IVF: in vitro fertilisation
TiDs: 3 times daily

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

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Brenner 1962	Outcomes of this study were not applicable to this review. Treatment was not given to women until 38 weeks' gestation. The outcome measured was time from onset of labour to delivery
Check 1985	No method of randomization was used for this study.
Check 1987a	No method of randomization was used for this study.
Check 1987b	It is unclear as to whether there was any randomization. The authors of this review attempted, but failed, to contact the trial authors
Check 1995	The intervention considered in this study is progesterone in association with immunotherapy rather than progesterone alone
Clifford 1996	In this study, progesterone was not taken during pregnancy.
Daya 1988	This study is not an RCT.
Fuchs 1966	This study was terminated before the results were of sufficient size to statistically analyze. Therefore, data are incomplete
Johnson 1975	The outcome measure of this study was preterm delivery rather than miscarriage
Kyrou 2011	Comparison of stopping progestin at 12 weeks vs continuing. Wrong comparison
Norman 2006	This study was excluded because progesterone was given after 20 weeks' gestation to prevent preterm labour
Prietl 1992	The active intervention given in this study is a combination of progesterone and oestrogen, rather than progesterone alone
Rock 1985	This study is not an RCT.
Shu 2002	Wrong population and intervention.
Sidelnikova 1990	This study is not an RCT.
Smitz 1992	This study compares intramuscular progesterone versus intravaginal progesterone in the luteal phase followed by all participants receiving progesterone and oestrogen on the day prior to ovocyte puncture. There is no placebo or 'no treatment' control and the treatment given after commencement of pregnancy is a combination of progesterone and oestrogen rather than progesterone alone
Sondergaard 1985	This trial was conducted to ascertain the efficacy of progesterone to prevent preterm birth rather than miscarriage
Turner 1966	The outcome of this study is not relevant to the current systematic review. Progesterone was not given to prevent miscarriage and was not given until the 30/40

RCT: randomized controlled trial

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

VS: versus

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

Coomarasamy 2012

Trial name or title	PROMISE.
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Raddatz 2006

Trial name or title	Habitual abortion study.
Methods	
Participants	Pregnant women with history of 3 idiopathic miscarriages.
Interventions	Oral dydrogesterone versus placebo.
Outcomes	Change in IFN/IL-10 ratio.
Starting date	2003
Contact information	Gereon Raddatz, gereon.raddatz@solvay.com
Notes	

Walch 2005

Trial name or title	The prevention of miscarriage study (PROMISE).
Methods	
Participants	Pregnant women with history of at least 3 spontaneous miscarriages with same partner and negative standard evaluation

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Walch 2005 (*Continued*)

Interventions	20 mg daily oral dydrogesterone versus placebo tablet.
Outcomes	Change in Interferon-gamma/Interleukin-10 ratio from baseline and 'pregnancy outcomes'
Starting date	
Contact information	Dr. Katharina Walch, Vienna, Austria, katharina.walch@meduniwien.ac.at
Notes	

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DATA AND ANALYSES

Comparison 1. Progestogen versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Miscarriage (all trials)	14	2158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.78, 1.24]
2 Miscarriage (placebo controlled trials only)	14	2158	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.78, 1.24]
2.1 Trials with placebo control group	10	1028	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.88, 1.50]
2.2 Trials without placebo controls	4	1130	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.42, 1.02]
3 Miscarriage (women with previous recurrent miscarriage only)	10	1287	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.66, 1.07]
3.1 Women with a history of 3 or more prior miscarriages	4	225	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.21, 0.72]
3.2 Women with a history of 2 or more prior miscarriage	7	450	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.43, 1.07]
3.3 Women with unspecified prior miscarriages presenting with threatened miscarriage	3	612	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.84, 1.63]
4 Miscarriage (by route of administration versus placebo)	11	1600	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.65, 1.17]
4.1 Oral versus placebo/control	5	517	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.65, 1.40]
4.2 Intramuscular versus placebo/control	4	728	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.36, 1.68]
4.3 Vaginal versus placebo/control	2	355	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.40, 1.35]
5 Preterm birth	7	946	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.67, 1.81]
6 Neonatal death	5	445	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.72, 2.64]
7 Fetal genital abnormalities/virilisation	4	228	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.64 [0.15, 385.21]

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.1. Comparison 1 Progestogen versus placebo/no treatment, Outcome 1 Miscarriage (all trials).

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 1 Miscarriage (all trials)

Study or subgroup	Progestogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Berle 1980	58/154	46/146		23.4 %	1.31 [0.82, 2.11]
Corrado 2002	4/311	3/273		2.4 %	1.17 [0.26, 5.21]
El-Zibdeh 2005	11/82	14/48		6.5 %	0.37 [0.15, 0.90]
Gerhard 1987	3/26	5/26		2.4 %	0.56 [0.13, 2.49]
Goldzieher 1964	5/23	5/31		2.8 %	1.44 [0.36, 5.70]
Klopper 1965	8/18	5/15		2.8 %	1.57 [0.39, 6.25]
Le Vine 1964	4/15	8/15		2.6 %	0.34 [0.08, 1.44]
MacDonald 1972	3/20	3/20		1.8 %	1.00 [0.18, 5.55]
Moller 1965	63/123	66/137		22.3 %	1.13 [0.69, 1.84]
Nyboe Anderson 2002	18/153	22/150		11.9 %	0.78 [0.40, 1.51]
Reijnders 1988	2/32	1/32		1.0 %	1.99 [0.20, 19.86]
Shearman 1963	5/27	5/23		2.8 %	0.82 [0.21, 3.25]
Swyer 1953	11/60	13/53		6.5 %	0.69 [0.28, 1.70]
Tognoni 1980	26/74	21/71		11.0 %	1.29 [0.64, 2.57]
Total (95% CI)	**1118**	**1040**		**100.0 %**	**0.99 [0.78, 1.24]**

Total events: 221 (Progestogen), 217 (Placebo)

Heterogeneity: Chi^2 = 11.85, df = 13 (P = 0.54); I^2 =0.0%

Test for overall effect: Z = 0.13 (P = 0.90)

Test for subgroup differences: Not applicable

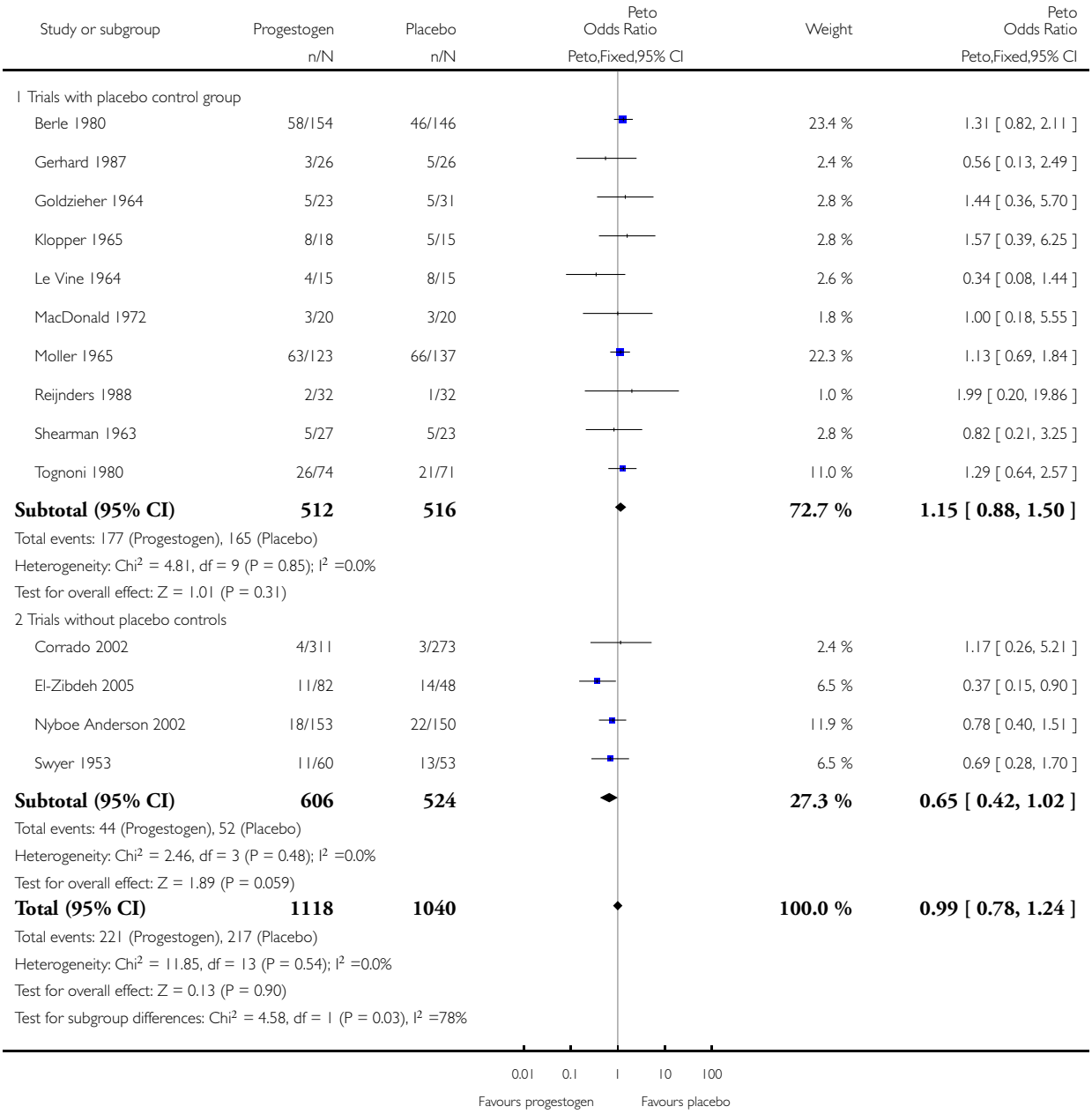
Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.2. Comparison 1 Progestogen versus placebo/no treatment, Outcome 2 Miscarriage (placebo controlled trials only).

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 2 Miscarriage (placebo controlled trials only)



Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

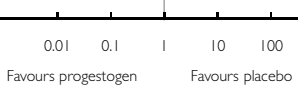
Analysis 1.3. Comparison 1 Progestogen versus placebo/no treatment, Outcome 3 Miscarriage (women with previous recurrent miscarriage only).

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 3 Miscarriage (women with previous recurrent miscarriage only)

Study or subgroup	Progestogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Women with a history of 3 or more prior miscarriages					
El-Zibdeh 2005	11/82	14/48		7.4 %	0.37 [0.15, 0.90]
Goldzieher 1964	2/8	4/10		1.6 %	0.53 [0.08, 3.59]
Le Vine 1964	4/15	8/15		2.9 %	0.34 [0.08, 1.44]
Swyer 1953	7/27	9/20		4.1 %	0.44 [0.13, 1.46]
Subtotal (95% CI)	**132**	**93**		**16.1 %**	**0.39 [0.21, 0.72]**
Total events: 24 (Progestogen), 35 (Placebo)					
Heterogeneity: Chi^2 = 0.18, df = 3 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 3.00 (P = 0.0027)					
2 Women with a history of 2 or more prior miscarriage					
El-Zibdeh 2005	11/82	14/48		7.4 %	0.37 [0.15, 0.90]
Goldzieher 1964	5/23	5/31		3.2 %	1.44 [0.36, 5.70]
Klopper 1965	8/18	5/15		3.1 %	1.57 [0.39, 6.25]
Le Vine 1964	4/15	8/15		2.9 %	0.34 [0.08, 1.44]
MacDonald 1972	3/20	3/20		2.0 %	1.00 [0.18, 5.55]
Shearman 1963	5/27	5/23		3.2 %	0.82 [0.21, 3.25]
Swyer 1953	11/60	13/53		7.4 %	0.69 [0.28, 1.70]
Subtotal (95% CI)	**245**	**205**		**29.3 %**	**0.68 [0.43, 1.07]**
Total events: 47 (Progestogen), 53 (Placebo)					
Heterogeneity: Chi^2 = 5.53, df = 6 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 1.68 (P = 0.093)					
3 Women with unspecified prior miscarriages presenting with threatened miscarriage					
Berle 1980	58/154	46/146		26.6 %	1.31 [0.82, 2.11]
Gerhard 1987	3/26	5/26		2.7 %	0.56 [0.13, 2.49]



(*Continued . . .*)

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(. . . *Continued*)

Study or subgroup	Progestogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Moller 1965	63/123	66/137		25.4 %	1.13 [0.69, 1.84]
Subtotal (95% CI)	**303**	**309**		**54.7 %**	**1.17 [0.84, 1.63]**
Total events: 124 (Progestogen), 117 (Placebo)					
Heterogeneity: Chi^2 = 1.18, df = 2 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.94 (P = 0.35)					
Total (95% CI)	**680**	**607**		**100.0 %**	**0.84 [0.66, 1.07]**
Total events: 195 (Progestogen), 205 (Placebo)					
Heterogeneity: Chi^2 = 17.61, df = 13 (P = 0.17); I^2 =26%					
Test for overall effect: Z = 1.41 (P = 0.16)					
Test for subgroup differences: Chi^2 = 10.73, df = 2 (P = 0.00), I^2 =81%					

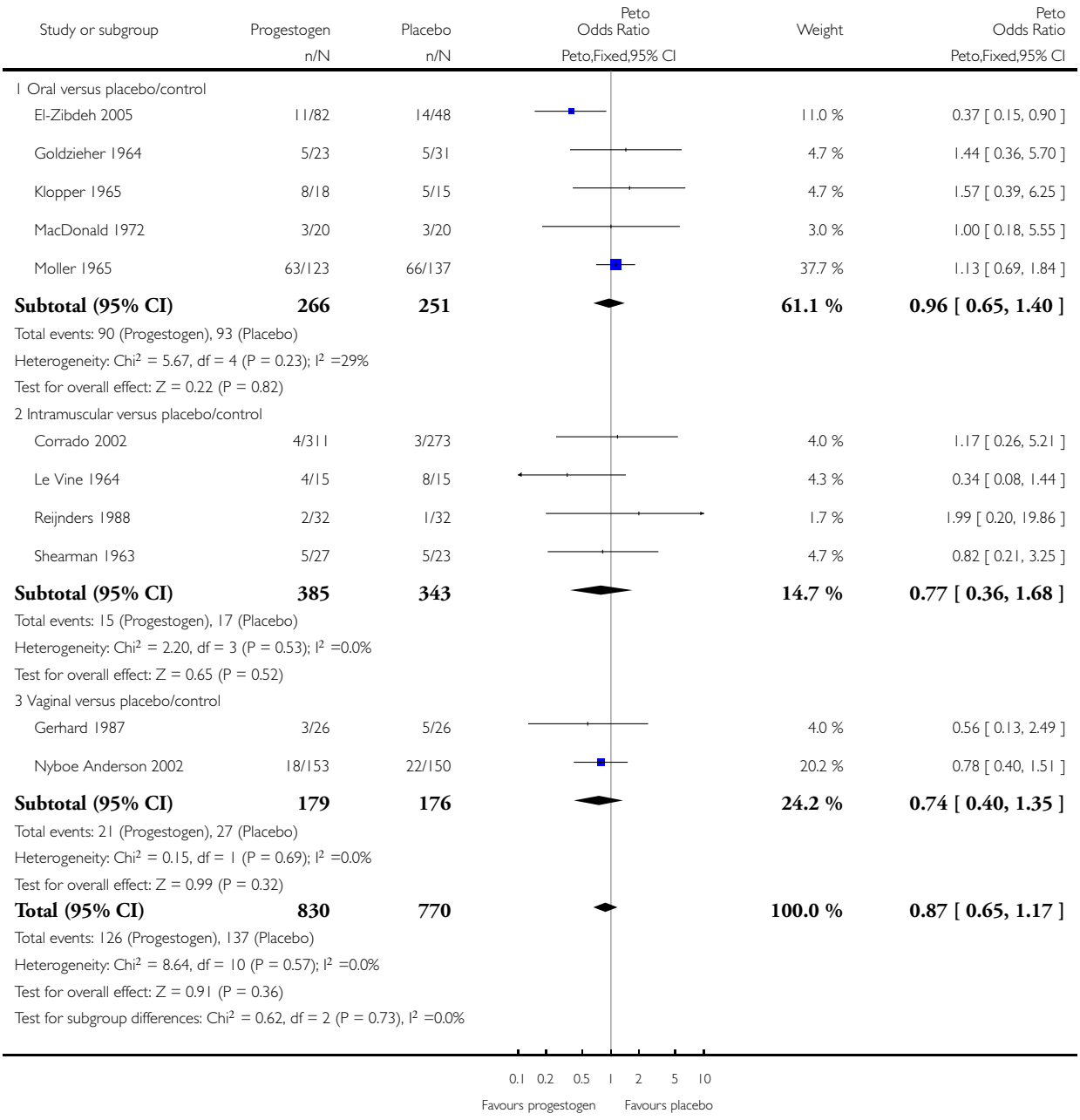
Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.4. Comparison 1 Progestogen versus placebo/no treatment, Outcome 4 Miscarriage (by route of administration versus placebo).

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 4 Miscarriage (by route of administration versus placebo)



Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.5. Comparison 1 Progestogen versus placebo/no treatment, Outcome 5 Preterm birth.

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 5 Preterm birth

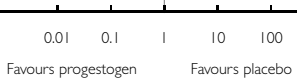
Study or subgroup	Progestogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Corrado 2002	27/311	20/273		68.6 %	1.20 [0.66, 2.18]
El-Zibdeh 2005	5/71	3/34		10.4 %	0.78 [0.17, 3.61]
Gerhard 1987	0/23	2/21		3.1 %	0.12 [0.01, 1.94]
Goldzieher 1964	1/18	1/26		3.0 %	1.47 [0.08, 25.46]
Le Vine 1964	6/11	3/7		7.2 %	1.56 [0.25, 9.81]
Reijnders 1988	1/31	1/31		3.1 %	1.00 [0.06, 16.36]
Swyer 1953	2/49	1/40		4.6 %	1.62 [0.16, 16.14]
Total (95% CI)	**514**	**432**		**100.0 %**	**1.10 [0.67, 1.81]**

Total events: 42 (Progestogen), 31 (Placebo)

Heterogeneity: Chi^2 = 3.01, df = 6 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 0.39 (P = 0.70)

Test for subgroup differences: Not applicable



Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.6. Comparison 1 Progestogen versus placebo/no treatment, Outcome 6 Neonatal death.

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 6 Neonatal death

Study or subgroup	Progestogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
El-Zibdeh 2005	2/71	1/34		7.1 %	0.96 [0.08, 11.00]
Gerhard 1987	0/23	0/21			Not estimable
Reijnders 1988	1/30	0/32		2.7 %	7.90 [0.16, 398.87]
Swyer 1953	1/49	0/40		2.7 %	6.15 [0.12, 316.22]
Tognoni 1980	26/74	21/71		87.5 %	1.29 [0.64, 2.57]
Total (95% CI)	**247**	**198**		**100.0 %**	**1.38 [0.72, 2.64]**

Total events: 30 (Progestogen), 22 (Placebo)

Heterogeneity: Chi^2 = 1.44, df = 3 (P = 0.70); I^2 =0.0%

Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable

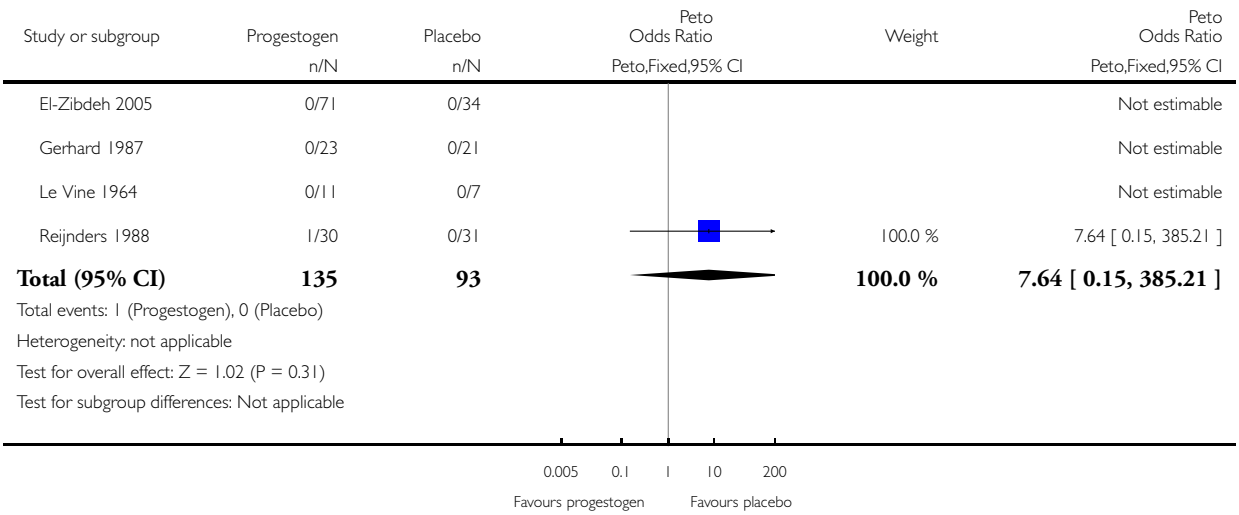
Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.7. Comparison 1 Progestogen versus placebo/no treatment, Outcome 7 Fetal genital abnormalities/virilisation.

Review: Progestogen for preventing miscarriage

Comparison: 1 Progestogen versus placebo/no treatment

Outcome: 7 Fetal genital abnormalities/virilisation



APPENDICES

Appendix 1. Search Methods used in previous versions of this review

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (January 2008).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, authors searched:

MEDLINE: 1966 to June 2006;

EMBASE: 1980 to June 2006;

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CINAHL: 1982 to June 2006.
See below for search strategy used.
We adapted the search strategy to search Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 4).
We searched the following trial registers:
NHMRC Clinical Trials Register (June 2006);
Meta-Register (June 2006).
Search strategy for MEDLINE, EMBASE and CINAHL (OVID)
1. miscarriage/
2. miscarriage$
3. spontaneous abortion
4. spontaneous pregnancy loss
5. fetal death
6. foetal death
7. recurrent ADJ miscarriage$
8. recurrent ADJ abortion$
9. recurrent ADJ pregnancy loss
10. recurrent ADJ fetal death
11. recurrent ADJ foetal death
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
13. progesterone
14. progestogen
15. progestogen$
16. preventative ADJ3 progesterone
17. preventative ADJ3 progestogen$
18. prophylactic ADJ3 progesterone
19. prophylactic ADJ3 progestogen$
20. prophylactic ADJ3 treatment
21. preventative ADJ3 treatment
22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 12 and 22

Appendix 2. Methods used to assess trials included in previous versions of this review

The following methods were used to assess Berle 1980; Corrado 2002; El-Zibdeh 2005; Gerhard 1987; Goldzieher 1964; Klopper 1965; Le Vine 1964; Moller 1965; Moller 1965b; Moller 1965c; Nyboe Anderson 2002; Reijnders 1988; Shearman 1963; Swyer 1953; Tognoni 1980.

Selection of studies

We assessed for inclusion all potential studies identified as a result of the search strategy. We resolved any disagreement through discussion. The selection of trials for inclusion in the initial review (Oates-Whitehead 2003) was performed by the two review authors (Richmal Oates-Whitehead and Judith Carrier) after employing the search strategy described previously. The lead review author, David M Haas, assessed the trials for inclusion in the updated review following the search strategy described previously.

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the Cochrane Handbook (Higgins 2005). Methods used for generation of the randomization sequence are described for each trial.

(1) Selection bias (allocation concealment)

We assigned a quality score for each trial, using the following criteria:

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(A) adequate concealment of allocation: such as telephone randomization, consecutively numbered sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
(C) inadequate concealment of allocation: such as open list of random number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, e.g. withdrawals, dropouts, protocol deviations)

We assessed completeness to follow-up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9% loss of participants;
(C) 10% to 19.9% loss of participants;
(D) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:
(A) blinding of participants (yes/no/unclear);
(B) blinding of caregiver (yes/no/unclear);
(C) blinding of outcome assessment (yes/no/unclear).
The quality and methodology of all studies, which were deemed eligible for the initial review, were then assessed independently by two review authors. Discrepancies were to be resolved by discussion but this proved unnecessary. Included trials were analyzed for the following quality criteria and methodological details. For the updated review, the lead review author assessed the eligibility of the quality and methodology of the study. This information is presented in the 'Characteristics of included studies' table and provides a context for discussing the reliability of results.

Trial characteristics

1. Method of randomization
2. Presence or absence of blinding to treatment allocation
3. Quality of allocation concealment
4. Number of women randomized, excluded or lost to follow-up
5. Whether an intention-to-treat analysis was done
6. Whether a power calculation was done
7. Duration, timing and location of the study

Characteristics of the study participants

1. Age and any other recorded characteristics of women in the study
2. Gestational stage
3. Gravida and parity

Interventions used

1. Synthetic or natural progestogen
2. Route of administration
3. Dose
4. Timing of administration

If the method of randomization was unclear from the original paper, every attempt was made to contact the authors of the original studies. However, due to the age of the studies, contact was rarely possible. Where randomization is stated, but the method of randomization could not be confirmed with the authors, the study has been treated as quasi-randomized in the analysis. If it was unclear as to whether any randomization, quasi or otherwise, had occurred and the authors of the trials could not be contacted, we excluded these papers from the review.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Data extraction and management

We designed a form to extract data. Two review authors extracted the data using the agreed form. We resolved discrepancies through discussion. We used the Review Manager software (RevMan 2003) to double enter all the data or a sub-sample.

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2003). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar.

Dichotomous data

For dichotomous data, results for each study were expressed as an odds ratio with 95% confidence intervals and combined for meta-analysis with RevMan software (RevMan 2003) using the Peto-modified Mantel-Haenszel method. The summary statistics were calculated using both the fixed-effect and a random-effects model with no statistical difference in results being shown between the two methods. The results shown in the 'Comparison and data table' section of this review are presented using the fixed-effect model.

Continuous data

It was planned that continuous differences between groups in the meta-analysis would be expressed as a weighted mean difference and 95% confidence interval. However, no continuous data were reported.

Unit of analysis issues

Cluster-randomized trials

There were no cluster-randomized trials. All trials randomized individuals.

Cross-over trials

There were no cross-over trials.

Available case analysis

We analyzed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If, in the original reports, participants were not analyzed in the group to which they were randomized, and there was sufficient information in the trial report, we attempted to restore them to the correct group.

Assessment of heterogeneity

We applied tests of heterogeneity between trials, if appropriate, using the I^2 statistic. When high levels of heterogeneity were identified among the trials (exceeding 50%), we explored it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis was used as an overall summary if this was considered appropriate.

Subgroup analyses

We conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.
We carried out the following subgroup analyses: placebo controlled trials only; women who had at least three consecutive miscarriages; oral progestogen versus placebo; intramuscular progestogen versus placebo; and vaginal progestogen versus placebo.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sensitivity analyses

We carried out sensitivity analysis to explore the effect of trial quality. This involved analysis based on an A, B, C, or D rating of selection bias and attrition bias. We excluded studies of poor quality in the analysis (those rating B, C, or D) in order to assess for any substantive difference to the overall result.

WHAT'S NEW

Last assessed as up-to-date: 3 September 2013.

Date	Event	Description
1 August 2013	New citation required but conclusions have not changed	No changes to conclusions.
1 August 2013	New search has been performed	Search updated and four new trials identified. One was included (MacDonald 1972), two excluded (Kyrou 2011; Shu 2002), and one is ongoing (Coomarasamy 2012). Three previously included trials (Moller 1965a; Moller 1965b; Moller 1965c) are in fact three separate reports from one trial (Moller 1965).

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 4, 2003

Date	Event	Description
12 May 2009	Amended	Contact details updated.
11 February 2008	Amended	Converted to new review format.
31 January 2008	New search has been performed	Search updated. Four new trials identified: we included El-Zibdeh 2005 and excluded Norman 2006. Two are ongoing (Raddatz 2006; Walch 2005). The inclusion of El-Zibdeh 2005 narrows the confidence intervals (CI) of the outcomes it contained, including narrowing the CI for women with a history of three or more miscarriages; thus leading to the strengthening of the conclusions somewhat
31 January 2008	New citation required but conclusions have not changed	This update has been prepared by a new review team.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CONTRIBUTIONS OF AUTHORS

David Haas: is the guarantor of the review; prepared the 2013 update; performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

Patrick Ramsey: performed independent data extraction and quality assessment of included trials for the updates; commented on the drafts for this update.

DECLARATIONS OF INTEREST

None known related to the review topic. A portion of Dr Haas's time and effort are supported by a grant from the US National Institutes of Health Obstetric-Fetal Pharmacology Units research network grant #5U10HD063094.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Habitual [prevention & control]; Abortion, Spontaneous [*prevention & control]; Pregnancy Trimester, Second; Progestins [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.