Progestogen for preventing miscarriage (Review)

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Progestogen for preventing miscarriage

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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 fertilised 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 strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (January 2008), CENTRAL (*The Cochrane Library* 2006, Issue 4), MEDLINE (1966 to June 2006), EMBASE (1980 to June 2006), CINAHL (1982 to June 2006), NHMRC Clinical Trials Register (June 2006) and Meta-Register (June 2006). We searched references from relevant articles, attempting to contact authors where necessary, and contacted experts in the field for unpublished works.

Selection criteria

Randomised 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

Fifteen trials (2118 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) 0.98; 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.

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

0.38; 95% CI 0.20 to 0.70). No statistically significant differences were found between the route of administration of progestogen (oral, intramuscular, vaginal) versus placebo or no treatment.

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

No evidence that progestogen can prevent miscarriage.

Hormones called progestogens prepare the womb (uterus) to receive and support the newly fertilised egg. It has been suggested that some women who miscarry may not make enough progesterone, so supplementing with progesterone has been suggested as a possible way to prevent miscarriage. This review of fifteen trials (2118 women) found no evidence that progestogens can prevent miscarriage in general. There was evidence, however, that women who have suffered three or more miscarriages may benefit from progestogen during pregnancy but more trials are needed and are under way, particularly where potential adverse effects on the baby are measured.

BACKGROUND

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 (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).

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).

Progesterone, a female sex hormone, is known to induce secretory changes in the lining of the uterus essential for successful implantation of a fertilised 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 fertilised 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 approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but due to some reports stating these drugs induce mild virilisation (masculinisation) of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it has been recommended that progesterone containing drugs be avoided in the first three months of pregnancy (Health 2001; Mosby 2001) .

Several Cochrane Reviews have been initiated to investigate different interventions for the prevention of miscarriage (Bamigboye 2003; Drakeley 2003; Lede 2005; Rumbold 2005; Porter 2006; Scott 1996). 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

Randomised or quasi-randomized trials comparing progestogens with placebo or no treatment, given for the prevention of miscarriage, were eligible for inclusion.

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.

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 Groups Trials Register by contacting the Trials Search Co-ordinator (January 2008).

The Cochrane Pregnancy and Childbirth Groups 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 we searched:

MEDLINE: 1966 to June 2006;

EMBASE: 1980 to June 2006;

CINAHL: 1982 to June 2006.

See Appendix 1 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).

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

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 (CDSR 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:
(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 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.

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, we will present results as summary relative risk with 95% confidence intervals. 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 eventuated.

Unit of analysis issues

Cluster-randomised 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.

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.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
Fifteen trials (2118 women) are included. For details of included and excluded studies, *see* the tables of 'Characteristics or included studies' and 'Characteristics of excluded studies'.

Trials excluded from the review

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). Four studies had outcomes that were irrelevant to the current review (Brenner 1962; Johnson 1975; Sondergaard 1985; Turner 1966), two used progestogen combination therapy rather than progestogen alone (Check 1995; Prietl 1992), 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).

Trials included in the review

Trial design characteristics

Interventions

Route of administration

Six studies administered treatment orally (El-Zibdeh 2005 ; Goldzieher 1964; Klopper 1965; Moller 1965a; Moller 1965b; Moller 1965c); 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 three studies used a staggered dose of medroxyprogesterone (20 mg/day for three days, followed by 10 mg/day for eleven days) (Moller 1965a; Moller 1965b; Moller 1965c). One study used a twice daily dose of cyclopentyl enol ether of progesterone (Enol Luteovis) (Klopper 1965), while the last used twice daily 10 mg tablets of dydrogesterone (El-Zibdeh 2005).

In the four studies which 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 eleven 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 which 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); three studies continued treatment for 14 days (Corrado 2002; Moller 1965a ; Moller 1965b); one study continued treatment for 17 days (Moller 1965c); 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 four studies treatment duration was either not stated or unclear (Berle 1980; Goldzieher 1964; Klopper 1965; Swyer 1953).

Placebo/control

Eleven of the included studies compared treatment with placebo (Berle 1980 ; Gerhard 1987 ; Goldzieher 1964 ; Klopper 1965 ; Le Vine 1964 ; Moller 1965a ; Moller 1965b ; Moller 1965c ; 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 (Le Vine 1964 ; El-Zibdeh 2005), and four trials required women to have suffered two or more consecutive miscarriages (Goldzieher 1964; Klopper 1965; Shearman 1963; Swyer 1953). Seven trials accepted women with threatened imminent pregnancy loss, whether or not they had a history of previous pregnancy loss (Berle 1980; Gerhard 1987; Moller 1965a; Moller 1965b; Moller 1965c; Reijnders 1988; Tognoni 1980). The remaining two studies (Corrado 2002; Nyboe Anderson 2002) enrolled women who had had amniocentesis and in vitro fertilisation respectively, regardless of obstetric history.

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

Gestation

Eight studies only accepted women within the first trimester of pregnancy (El-Zibdeh 2005; Gerhard 1987; Klopper 1965; Nyboe Anderson 2002 ; Reijnders 1988 ; Shearman 1963 ; Swyer 1953 ; Tognoni 1980), while three studies accepted women to the twentieth 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 1965a; Moller 1965b; Moller 1965c).

Studied outcomes

- Miscarriage: all 15 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: one paper which included three arms (Moller 1965a; Moller 1965b; Moller 1965c), and four other separate studies (El-Zibdeh 2005; Le Vine 1964; Reijnders 1988; Gerhard 1987) 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 gm: 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 four studies (Le Vine 1964; Moller 1965a; Moller 1965b; Moller 1965c).
- 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

Five studies reported support or sponsorship from pharmaceutical companies (Goldzieher 1964; Moller 1965a; Moller 1965b; Moller 1965c; Shearman 1963).

Risk of bias in included studies

Randomisation/quasi randomization

Of the 15 studies that met the inclusion criteria, one study used sequentially numbered ampules provided by the pharmaceutical company (Reijnders 1988); three studies used ampules or bottles coded 'A' or 'B' by an unknown source (Goldzieher 1964; Le Vine 1964; Shearman 1963); one used a random table produced by a statistician (Klopper 1965); one used a computer-generated randomization list using clusters of ten (Nyboe Anderson 2002); one used alternation (Berle 1980); three allocated women by odd and even admission number (Moller 1965a; Moller 1965b; Moller 1965c); one randomized by day of the week (El-Zibdeh 2005); while the randomization of three studies was unclear from the papers (Corrado 2002; Gerhard 1987; Tognoni 1980). In the final study (Swyer 1953), two centres took part. One centre allocated by alternation, while the paper states that the other used "randomization". However, the method of randomization is not stated.

Concealment of allocation

One study displayed adequate allocation concealment (Reijnders 1988); in two studies allocation concealment was clearly inadequate (Berle 1980; Swyer 1953); while the allocation in the remaining 12 studies was unclear (Corrado 2002; El-Zibdeh 2005; Gerhard 1987; Goldzieher 1964; Le Vine 1964; Klopper 1965; Moller 1965a; Moller 1965b; Moller 1965c; Nyboe Anderson 2002; Shearman 1963; Tognoni 1980).

Blinding

Nine 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; Moller 1965a; Moller 1965b; Moller 1965c; Reijnders 1988; Shearman 1963). It was unclear whether any blinding was used in the six remaining included studies (Berle 1980; Corrado 2002; El-Zibdeh 2005; Nyboe Anderson 2002; Swyer 1953; Tognoni 1980).

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 centres

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

Withdrawals and intention-to-treat analysis

Of the four studies that reported withdrawals or exclusions (Corrado 2002; Gerhard 1987; Le Vine 1964; Tognoni 1980), no study performed an intention-to-treat analysis.

Dropouts

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.

Effects of interventions

Fifteen trials (2118 women) met the inclusion criteria.

Progestogen versus placebo or control to prevent miscarriage

The meta-analysis of the 15 included studies (2118 women) showed no statistically significant difference in miscarriage rates between progestogen and placebo groups (Peto odds ratio (Peto OR) 0.98; 95% confidence interval (CI) 0.78 to 1.24).

A sensitivity analyses was performed excluding studies 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 0.87 to 1.51).

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 0.38; 95% CI 0.20 to 0.70).

Oral progestogen versus placebo

Five studies compared oral progestogen with placebo (Goldzieher 1964; Klopper 1965; Moller 1965a; Moller 1965b; Moller 1965c). The meta-analysis showed no statistically significant difference in miscarriages between the progestogen and placebo group (Peto OR 1.11; 95% CI 0.79 to 1.56).

Intramuscular progestogen versus placebo

Four studies compared intramuscular progestogen with placebo (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).

Vaginally administered progestogen versus placebo/control

One study compared vaginally administered progestogen with placebo (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).

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). In addition, the three arms of Moller et al (Moller 1965a; Moller 1965b; Moller 1965c) reported 18 preterm births but failed to give data on how these were divided between the progestogen and placebo groups.

Neonatal death

Four 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 remaining two (Reijnders 1988; Swyer 1953) showed no significant difference between treatment and placebo (Peto OR 2.27; 95% CI 0.36 to 14.23). In addition, the three arms of Moller et al (Moller 1965a; Moller 1965b; Moller 1965c) 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 gm. 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.

Fetal abnormalities

Four studies reported fetal abnormalities as an outcome (El-Zibdeh 2005; Gerhard 1987; Reijnders 1988; Le Vine 1964). 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). 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 three arms of Moller et al (Moller 1965a; Moller 1965b; Moller 1965c) 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

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

DISCUSSION

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. Two trials are currently underway to further evaluate therapy in this subgroup of women.

The meta-analysis showed no statistically significant difference in the number of fetal abnormalities (including virilisation 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.

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.

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* *Indicates the major publication for the study*

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 centres: 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.

Berle 1980

(*Continued*)	
	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

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

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 centres: 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

Item	Authors' judgement	Description

Corrado 2002

(*Continued*)

Allocation concealment?	Unclear	B - Unclear

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 centres: 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 12the gestational week.
Outcomes	Miscarriage, preterm delivery, fetal malformations, perinatal death (not analysed in review: hospitalisation for vaginal bleeding).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Gerhard 1987

Methods	Unit of randomisation: pregnancy. Method of randomisation: unclear. Timing of randomisation: before the 13th week of gestation. Blinding: yes (double). Power calculation: yes (95% of 32 women were randomised to each group). Number of centres: 1. 64 women randomised. 8 women excluded. 56 women analysed.

Gerhard 1987

(*Continued*)	
	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Goldzieher 1964

Methods	Unit of randomisation: pregnancy. Method of randomisation: sequentially-numbered bottles. It is not clear who was responsible for the coding. Timing of randomisation: unclear. Blinding: yes (double). Power calculation: nil. Number of centres: 2 main centres. 54 women randomised, 0 women excluded, 54 women analysed. 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.

Goldzieher 1964

(*Continued*)

	Preterm delivery.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Klopper 1965

Methods	Unit of randomisation: pregnancy. Method of randomisation: random schedules generated by a statistician. Timing of randomisation: before 10 weeks gestation. Power calculation: nil. Blinding: yes (double). Number of centres: 2. 33 women randomised, 33 women analysed. 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Le Vine 1964

Methods	Unit of randomisation: pregnancy. Method of randomisation: 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 randomisation: within the 16th week of pregnancy. Power calculation: nil. Blinding: yes (double).

Le Vine 1964

(*Continued*)	
	Number of centres: not stated. 56 women randomised, 26 women excluded, 30 women analysed. 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.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Moller 1965a

Methods	Unit of randomisation: pregnancy. Method of randomisation: odd and even admission numbers. Timing of randomisation: unclear. Power calculation: nil. Blinding: yes (double). Number of centres: 1. 40 women randomised, 0 women excluded, 40 women analysed. Source of funding: preparations were supplied by Leo Pharmaceuticals.
Participants	Women with a positive pregnancy test. Age: 3 studies (Moller 1965a, Moller 1965b, and Moller 1965c) were reported in one paper. A breakdown of the ages for each part has not been given. Location: Denmark.
Interventions	20 mg/day of oral medroxyprogesterone for 3 days, followed by 10 mg/day for 11 days. Placebo: yes.
Outcomes	Miscarriage. Side effects of treatment suffered by the mother. Genital abnormalities.

Moller 1965a

(*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Moller 1965b

Methods	Unit of randomisation: pregnancy. Method of randomisation: odd and even admission numbers. Timing of randomisation: unclear. Power calculation: nil. Blinding: yes (double). Number of centres: 1. 63 women randomised, 0 women excluded, 63 women analysed. Source of funding: preparations were supplied Leo Pharmaceuticals.
Participants	Women with a positive pregnancy test. Age: 3 studies (Moller 1965a, Moller 1965b, and Moller 1965c) were reported in one paper. A breakdown of the ages for each part has not been given. Location: Denmark
Interventions	40 mg/day of oral medroxyprogesterone for 3 days, followed by 20 mg/day for 11 days. Placebo: yes. Timing: 1961-1962.
Outcomes	Miscarriage. Side effects of treatment suffered by the mother. Genital abnormalities.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Moller 1965c

Methods	Unit of randomisation: pregnancy. Method of randomisation: odd and even admission numbers.

Moller 1965c

(*Continued*)	
	Timing of randomisation: unclear. Power calculation: nil. Blinding: yes (double). Number of centres: 1. 153 women randomised, 0 women excluded, 153 women analysed. Source of funding: preparations were supplied by Leo Pharmaceuticals.
Participants	Women with a positive pregnancy test. Age: 3 studies (Moller 1965a, Moller 1965b, and Moller 1965c) were reported in 1 paper. A breakdown of the ages for each part has not been given. Location: Denmark.
Interventions	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. Timing: 1962-1964.
Outcomes	Miscarriage. Side effects of treatment suffered by the mother. Genital abnormalities.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nyboe Anderson 2002

Methods	Unit of randomisation: pregnancy. Method of randomisation: computer-generated randomisation list. Timing of randomisation: 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 centres: 2. 303 women randomised, 0 excluded, 303 women analysed. 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. Location: Denmark. Timing and duration: 1999-2000.
Interventions	200 mg TiDs vaginal suppositories. Placebo: no control group received no treatment. Duration: 3 weeks.

Nyboe Anderson 2002

(*Continued*)	
Outcomes	Miscarriage.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Reijnders 1988

Methods	Unit of randomisation: pregnancy. Method of randomisation: sequentially-coded ampules supplied be the drug company. Timing of randomisation: 6-7 weeks' gestation. Blinding: yes (double). Number of centres: not stated. Power calculation: yes (80% with 40 in each group). 64 women randomised, 0 women excluded, 64 women analysed. 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Shearman 1963

Methods	Unit of randomisation: pregnancy. Method of randomisation: 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 randomisation: before the 12th week of gestation. Blinding: yes (double). Power calculation: nil. Number of centres: 2. 50 women randomised. 0 women excluded. 50 women analysed. 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Swyer 1953

Methods	Unit of randomisation: pregnancy. Method of randomisation of allocation: there were 2 centres in this study. 1 allocated by alternation. It was stated in the paper that the other centre used "randomisation". However, method of randomisation is not given. Timing of randomisation: before 12 weeks' gestation. Blinding: unclear. Power calculation: nil. Number of centres: 2. 113 women were enrolled, 0 women were excluded, 113 women were analysed. Source of funding: not stated.

Swyer 1953

(*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Tognoni 1980

Methods	Unit of randomisation: pregnancy. Method of randomisation: unknown. Timing of randomisation: up until the 14th week of gestation. Blinding: unclear. Power calculation: nil. Number of centres: 12. Number of women randomised: 145. Number of exclusions 6. Number of women analysed: 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

Tognoni 1980

(*Continued*)	
	25 mg IM hydroxyprogesterone caproate every 5 days. Placebo: yes. Duration: 8 weeks.
Outcomes	Miscarriage.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

[a] BiD: twice daily
CI: confidence interval
ICSI: intracytoplasmic sperm injection
IM: intramuscular
IVF: in vitro fertilisation
TiDs: 3 times daily

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

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 randomisation was used for this study.
Check 1987a	No method of randomisation was used for this study.
Check 1987b	It is unclear as to whether there was any randomisation. 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 analyse. Therefore, data are incomplete.
Johnson 1975	The outcome measure of this study was preterm delivery rather than miscarriage.
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

(*Continued*)

Study	Reason for exclusion
	progesterone alone.
Rock 1985	This study is not an RCT.
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.

[a] RCT: randomised controlled trial
VS: versus

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

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 (PROMIS).
Methods	
Participants	Pregnant women with history of at least 3 spontaneous miscarriages with same partner and negative standard

Walch 2005

(*Continued*)	
	evaluation.
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	

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)	15	2118	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.78, 1.24]
2 Miscarriage (placebo controlled trials only)	11	988	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.87, 1.51]
3 Miscarriage (women with previous recurrent miscarriage only)	4	223	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.20, 0.70]
4 Miscarriage (oral progestogen versus placebo)	5	563	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.79, 1.56]
5 Miscarriage (intramuscular progestogen versus placebo)	4	728	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.36, 1.68]
6 Miscarriage (vaginal progestogen versus placebo)	2	355	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.40, 1.35]
7 Preterm birth	7	946	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.67, 1.81]
8 Neonatal death	4	300	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.27 [0.36, 14.23]
9 Fetal genital abnormalities/virilisation	4	228	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.64 [0.15, 385.21]

WHAT'S NEW

Last assessed as up-to-date: 30 January 2008

Date	Event	Description
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.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 4, 2003

CONTRIBUTIONS OF AUTHORS

David Haas: is the guarantor of the review; prepared the 2008 update; performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the first version of the review.

Patrick Ramsey: commented on the drafts for this update.

DECLARATIONS OF INTEREST

None known.

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