Progestogen for treating threatened miscarriage (Review)

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ABSTRACT

Background
Miscarriage is a common complication encountered during pregnancy. The role of progesterone in preparing the uterus for the implantation of the embryo and its role in maintaining the pregnancy have been known for a long time. Inadequate secretion of progesterone in early pregnancy has been linked to the aetiology of miscarriage and progesterone supplementation has been used as a treatment for threatened miscarriage to prevent spontaneous pregnancy loss.

Objectives
To determine the efficacy and the safety of progestogens in the treatment of threatened miscarriage.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (December 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 1), MEDLINE (January 1966 to April 2006), EMBASE (1980 to April 2006) and CINAHL (1982 to April 2006). We scanned bibliographies of all located articles for any unidentified articles.

Selection criteria
Randomized or quasi-randomized controlled trials that compare progestogen with placebo, no treatment or any other treatment given in an effort to treat threatened miscarriage.

Data collection and analysis
At least two authors assessed the trials for inclusion in the review and extracted the data.

Main results
Two studies (84 participants) were included in the meta-analysis. In one study, all the participants met the inclusion criteria and in the other study, only the subgroup of participants who met the inclusion criteria was included in the meta-analysis. There was no evidence of effectiveness with the use vaginal progesterone compared to placebo in reducing the risk of miscarriage (relative risk 0.47; 95% confidence interval (CI) 0.17 to 1.30).

Authors' conclusions
Based on scarce data from two methodologically poor trials, there is no evidence to support the routine use of progestogens for the treatment of threatened miscarriage. Information about potential harms to the mother or child, or both, with the use of progestogens is lacking. Further, larger, randomized controlled trials on the effect of progestogens on the treatment of threatened miscarriage, which investigate potential harms as well as benefits, are needed.

PLAIN LANGUAGE SUMMARY

Progestogen for treating threatened miscarriage

Threatened miscarriage is when a mother might be losing her baby at less than 23 weeks' gestation. The signs are vaginal bleeding, with or without abdominal pain, while the cervix is closed. Once the cervix begins to open, miscarriage and pregnancy loss are inevitable.

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Miscarriage is common, happening in about 15% to 20% of pregnancies, and it can cause emotional problems in terms of depression, sleep disturbances, anger, etc. Miscarriage can also be associated with excessive bleeding and shock, and in low-income countries sometimes causes maternal death, though this is very rare in high-income countries. Progestogen is an essential hormone for establishing and maintaining pregnancy, and so is therefore thought to be a possible treatment for threatened miscarriage. The review of trials located just two studies, involving 84 women, that met the entry criteria but they were still poor quality studies. Hence, there is insufficient evidence to assess if progestogen is an effective treatment for threatened miscarriage. Any future studies should not only look at the possible impact on miscarriage and pregnancy, but also need to check there are no adverse effects on the baby.

BACKGROUND

Miscarriage is pregnancy loss before 23 weeks' gestation based on the first day of the last menstrual period (WHO 1992). Threatened miscarriage is manifested by vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus is viable and inside the uterine cavity (Cunningham 2001a). Once the cervix begins to dilate, miscarriage and pregnancy loss are inevitable. When the fetus is non-viable and the cervix is closed, this is known as missed miscarriage or missed abortion (Cunningham 2001a). The presence of a short cervix or funneling of the internal cervical os in the gestation period between 16 to 24 weeks has been found to indicate an increase risk or a threat to miscarry (Owen 2004; Rust 2005).

Miscarriage is a common complication of pregnancy occurring in 15% to 20% of all clinically recognized pregnancies (Everett 1997; Hemminki 1998; Huisjes 1984). It is associated with chromosomal abnormality of the conceptus in over 50% of cases (Burgoyne 1991; Szabo 1996). Other risk factors for miscarriage include maternal age over 34 years (Falco 1996), maternal infection such as genital herpes simplex, human immunodeficiency virus-1 and vaginal colonization of group B streptococci (Temmerman 1992). Maternal endocrine abnormalities such as uncontrolled diabetes mellitus (Greene 1999) and insufficient production of progesterone by the corpus luteum (Cunningham 2001a), polycystic ovary syndrome, maternal autoimmune factors such as phospholipids antibodies, and a previous history of two or more miscarriages (Brigham 1999) are other suggested factors associated with miscarriage. In many cases, the cause of miscarriage cannot be identified in a large number of women.

Miscarriage is associated with considerable physical and psychological morbidity. Bleeding can be excessive, leading to shock (McBride 1991) and death, a known complication in developing countries (Goyaux 2001) but very rare in developed countries (CE 1998). The emotional response to miscarriage can be profound; it includes depression, sleep disturbance, anger and marital disturbances (Dyregrove 1987). The introduction of ultrasound scans in the management of bleeding in early pregnancy has improved the diagnosis by rapid confirmation of viability and has improved the management by introducing prognostic factors such as fetal bradycardia and discrepancy between gestational age and crown-to-rump length (Makrydimas 2003). This has rationalized the management as attempts to maintain a pregnancy are likely to be effective only if the fetus is viable and has no chromosomal abnormalities (Lede 2005).

Progestogens are a group of hormones, which bind to the progesterone receptors; they include both the natural female sex hormone progesterone and the synthetic forms. Progesterone is secreted during early pregnancy from the ovary by corpus luteum (Cunningham 2001b). It is an essential hormone for the establishment and maintenance of pregnancy by inducing secretary changes in the lining of the uterus, which are important for implantation of the fertilized ovum (Cunningham 2001b). Progesterone modulates the immune response of the mother to prevent rejection of the embryo and it enhances uterine quiescence and suppresses uterine contractions (Meis 2004; Stites 1983).

Owing to the documented physiological role of progesterone in maintaining pregnancy, it has been used to treat women with threatened miscarriage and presumed progesterone deficiency to improve expectations for continuity of pregnancy (Palagiano 2004). The therapeutic value of progesterone in preventing or treating threatened miscarriage has not been established (Kalinka 2005; Oates-Whitehead 2003). This might be due to the poor designs of the studies done to evaluate its effectiveness (Kalinka 2005), and the inclusion of women in these trials with different etiologies for threatened miscarriage.

The importance of progesterone on the maintenance of pregnancy was demonstrated by the successful use of progesterone antagonists, such as mifepristone (RU 486) in the elective induction of abortion (Nielsen 1999; Tang 2003). In a recently published Cochrane review (Dodd 2006), intramuscular progesterone was associated with a reduction in the risk of preterm birth less than 37 weeks' gestation, and infant birthweight less than 2500 grams. This raised the question about the importance of the route of administration and the type of progestogen used to prevent preterm labour (Di Renzo 2005). These same questions might apply to the use of progestogens in the treatment of threatened miscarriage.

Progestogen therapy has been linked to the development of hypospadias (deformity of the penis) in the male fetus (Silver 1999); however, there is little evidence on teratogenicity (Oates-Whitehead 2003).

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The aim of this review is to study all the available data on the effectiveness of administration of progestogens for the treatment of threatened miscarriage.

OBJECTIVES

To assess the effectiveness and safety of progestogens in the treatment of threatened miscarriage.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials or quasi-randomized controlled trials that assess the effectiveness of progestogens in the treatment of threatened miscarriage compared to placebo, no treatment or other intervention, if viability of the embryo or the fetus is confirmed before the commencement of treatment.

Types of participants

All pregnant women, with threatened miscarriage at or less than 23 weeks and who have a confirmed viable pregnancy. Fetal viability is to ensure exclusion from this review of studies which included women with bleeding in early pregnancy due to missed miscarriage. No restriction was placed on the age of the woman or past obstetric history.

Types of intervention

All types of progestogens, natural or synthetic, used in the treatment of threatened miscarriage regardless of the dose, duration or route of administration compared with placebo, no treatment or other intervention.

Types of outcome measures

Primary outcomes

(1) Early miscarriage up to 12 weeks;
(2) miscarriage later than 12 weeks and less than 23 weeks.

Secondary outcomes

Mother

(1) Pain relief;
(2) thromboembolism;
(3) preterm deliver;
(4) depression;
(5) any other adverse outcomes that were reported.

Child

(1) Preterm birth;
(2) stillbirth;
(3) neonatal death;
(4) fetal structural malformations, including genital malformations;
(5) any other adverse neonatal outcomes that were reported.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pregnancy and Childbirth Group methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (December 2006).

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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 'Search strategies for identification of studies' 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 the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 1), MEDLINE (1966 to April 2006), EMBASE (1980 to April 2006) and CINAHL (1982 to April 2006). We used the following search strategy adapted for each database by selecting the appropriate subject headings and changing the proximity operators:

1. Abortion, threatened (subject heading)
2. miscarriage*
3. spontaneous near abortion
4. spontaneous near pregnancy loss
5. threatened near pregnancy loss
6. abortion near threatened
7. (vagina* near bleed*) and pregnan*
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Progesterone (subject heading)
10. Progestins (subject heading)
11. progesteron*
12. progestogen*

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13. progestin*
14. progestational next agent*
15. progestational next therap*
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 16 and 8

We did not apply any language restrictions.

METHODS OF THE REVIEW

We included trials that met the inclusion criteria detailed above. Two review authors assessed the trials for inclusion independently and any disagreement was resolved by discussion between all the review authors. Both review authors independently reviewed the full text of the identified articles, including those where there was disagreement in the initial title or abstract scanning, to ensure that the inclusion criteria were met. Where necessary, we contacted the author for additional information.

One review author identified articles from other sources (experts or reference lists) as possibly eligible and two authors then assessed them for inclusion independently as described above. Authors were not blinded to the journal of origin or institution. Two authors independently assessed the abstracts of non-English articles, which had been translated, to ascertain if they met the inclusion criteria. We obtained a translation of the full article for those that met the criteria except for one article which is pending evaluation.

We assessed the validity of each included trial according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). These included:

(1) Assessment of generation of randomization sequence and allocation concealment (selection bias). This was graded as:
(A) adequate such as telephone randomization;
(B) uncertain when the study does not report any concealment approach;
(C) inadequate such as use of dates of birth or days of the week.
Where the method of allocation concealment is unclear, attempts were made to contact authors to provide further details.

(2) We assessed blinding, (performance bias) 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).

(3) We assessed completeness to follow up (attrition bias) using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 10% loss of participants;
(C) more than 10% and less than 20% loss of participants;
(D) more than 20% loss of participants.
We excluded from the analysis data for the outcomes where more than 20% of participants were lost to follow up.

(4) Analysis by intention to treat.

Data extraction
We designed a form to extract data. At least 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 the data.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details. Statistical analysis was done using RevMan 2003. Results were presented as relative risk, risk difference and number needed to treat.

Measures of treatment effect
We carried out statistical analysis using RevMan 2003. We used a fixed-effect meta-analysis for combining data as trials were sufficiently similar.

Dichotomous data
For dichotomous data, we presented results as summary relative risk with 95% confidence intervals.

Continuous data
For continuous data, we used the weighted mean difference (only one study analysed).

The same method of analysis will be used in future updates of this review if outcomes are measured in the same way between trials, and we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods. If there is evidence of skewness, this will be reported.

We were unable to perform an intention-to-treat analysis in this review because of insufficient information from the original trials but for future updates of this review, we will analyze data on an intention-to-treat basis. Therefore, all participants with available data will be included in the analysis in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If, in the original reports, participants are not analysed in the group to which they were randomized, and there is sufficient information in the trial report, we will attempt to restore them to the correct group.

Unit of analysis issues

Cluster-randomized trials
We did not identify any cluster-randomized trials. For future updates of this review, we will include cluster-randomized trials in the analyses. Their sample sizes will be adjusted using the methods described in Gates 2005 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, this will be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesise the relevant information. We will consider it reasonable

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to combine the results from both if the sources of heterogeneity are relatively small 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 separate meta-analysis; therefore, the meta-analysis will be performed in two parts as well.

Assessment of heterogeneity

We did not need to assess heterogeneity in this review. For future updates of this review, we will apply tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis and perform a sensitivity analysis. A random-effects meta-analysis will be used as an overall summary if this is considered appropriate.

Sensitivity analyses

Only two studies of similar quality were included in this meta-analysis. For future updates of this review, we will carry out sensitivity analysis to explore the effect of trial quality. This will involve analysis based on an A, B, C or D rating of selection bias, performance bias and attrition bias. The results of high-quality studies will be compared with those of poorer quality studies, where studies rated A for all quality criteria will be compared with those rated B, C or D.

We will carry out sensitivity analysis to explore the effect of trial quality assessed by concealment of allocation by excluding studies with clearly inadequate allocation of concealment (rated C).

Subgroup analyses

Information from primary studies was not sufficient to perform subgroup analysis. For future updates of this review, should sufficient data become available, subgroup analysis will be done by type of progestogen, dose, and route of administration and effect of progestogens in early (no more than 12 weeks) and late (more than 12 weeks) threatened miscarriage.

DESCRIPTION OF STUDIES

Thirty-one studies were potentially eligible for inclusion in this review. Of these, two were included after applying the inclusion criteria stated above (Gerhard 1987; Palagiano 2004). Twenty-eight studies did not meet the inclusion criteria and one study is pending evaluation after translation (Zhang 2000).

Trials excluded from the review

On obtaining the full papers, 18 studies were found to have outcomes which were irrelevant to this review (Brenner 1962; Corrado 2002; El Zibdeh 2000; El Zibdeh 2002; El Zibdeh 2005; Fuchs 1966; Goldzieher 1964; Johnson 1975; Klopper 1965; Le Vine 1964; Nyboe 2002; Prietl 1992; Reijnders 1988; Shearman 1963; Smitz 1992; Sondergaard 1985; Swyer 1953; Turner 1966), and four studies were found to have used a combination therapy with progesterone rather than progesterone alone (Berle 1977; Check 1995; Crowder 1950; Luz 1988). In another four studies, the viability of the fetus was not confirmed by a reliable method such as ultrasound scanning before the commencement of the treatment (Berle 1980; G-Videtzky 1965; Moller 1965; Souka 1980; Tognoni 1980) and one study was excluded because more than 20% of the randomized participants were lost to follow up (Omar 2005).

See 'Characteristics of excluded studies' table for details of the excluded studies.

Trials included in this review

Two trials were included, involving 84 participants.

In the study by Gerhard et al (Gerhard 1987), 64 women were randomized, eight women were excluded and the remaining 56 women were analyzed; only a subgroup of 35 women was included in this review as they fulfilled the inclusion criteria of confirmation of fetal viability by ultrasound scan before commencement of treatment. The women were accepted to the trial in the first trimester of pregnancy and were randomized to treatment and placebo groups. The treatment group received 25 mg progesterone twice daily in the form of vaginal suppositories and the control group received a placebo. The intervention continued until the woman either miscarried or for 14 days after the bleeding stopped. The main outcomes of this study included miscarriage, birthweight and preterm labour. The subgroup of the 35 women from this study were analysed for the primary outcome as for the secondary outcomes such as preterm birth; data could not be extracted separately.

Palagiano 2004 evaluated 50 women with previous diagnosis of inadequate luteal phase, a current diagnosis of threatened miscarriage and confirmed fetal viability. Gestational age at the time of enrolment to the study was 6 to 12 weeks. The treatment group received 90 mg progesterone (Crinone® 8%) vaginal gel once daily and the control group received a placebo. The assessment of the pain was by a five-point scale. The duration of the intervention lasted five days. The women were followed for up to 60 days for the occurrence of miscarriage and for five days for the other outcomes, which were pain relief, frequency of uterine contractions and blood loss. The effect of progesterone on miscarriage rate was analysed as a primary outcome while its effect on pain relief could not be analysed because data were skewed.

Details of the two included studies are provided in the 'Characteristics of included studies' table. Both trials did not include data on the short or long-term adverse effect on the mother or the child.

METHODOLOGICAL QUALITY

In the Gerhard 1987 study, the method of randomization and the allocation concealment were unclear. The trial was double blinded

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and the power calculation was done with 95% confidence intervals. Sixty-four women were enrolled, but eight were excluded resulting in a dropout of 12% after randomization. An intention-to-treat analysis was not performed. Only one centre participated in this trial.

In the Palagiano 2004 study, the method of randomization was unclear but the allocation concealment was adequate; both the women and the team allocating the treatment were blinded to the treatment; the power calculation was done for pain relief but not for miscarriage. The dropout rate for participants was reported but the numbers were not specified and an intention-to-treat analysis was not done as participants who dropped out in both groups, obviously after randomization, were replaced to keep each arm of the trial at 25 participants. It was not clear from the study how participants who dropped out were replaced.

Both studies were therefore of poor methodological quality.

RESULTS

Two trials met the inclusion criteria, involving 85 participants. Due to a paucity of data, subgroup analysis for early and late miscarriage, effect of progestogen by type, dose, and route of administration could not be carried out (*see* RevMan Analyses).

Meta-analysis of the effect of vaginal progesterone on miscarriage compared to placebo showed a point estimate which suggests a reduction of miscarriage rate with the use of progesterone (relative risk (RR) 0.47; 95% confidence interval (CI) 0.17 to 1.30), but the uncertainty about it is wide due to the small sample size, and the data are compatible both with a large reduction in miscarriage and a fairly large increase.

No secondary outcomes could be analysed due to a lack of data from primary studies. Data on the effects of progesterone on pain from threatened miscarriage (Palagiano 2004) were not suitable for analysis because they were skewed. The other study (Gerhard 1987) did not evaluate pain relief as an outcome.

DISCUSSION

Progestogens have been investigated by many studies for more than half a century as therapeutic agents for the treatment of miscarriage, but the poor methodological qualities of these studies and the inclusion in the investigated population of women with undocumented fetal viability have resulted in uncertainties associated with the use of this hormone and its effect on miscarriage. The methodological qualities of the studies included in this review were unclear in some respects, such as methods of randomization (Gerhard 1987; Palagiano 2004) and allocation concealment (Gerhard 1987), which made the presence of selection bias a possibility we could not refute or confirm. We graded the Gerhard 1987 study as C in relation to attrition bias but it was not possible to grade the Palagiano 2004 study because the number of participants who dropped out was not specified, with the additional weakness that it was unclear where the replacements came from. Intention-to-treat analysis was not observed in either of the trials and we were unable to perform that due to the lack of necessary data. All these potential and confirmed biases affect the validity of the trials and put them in the methodologically-poor category.

From the analysis, the point estimate suggested reduction in the miscarriage rate with the use of progesterone. However, due to the small sample size, the confidence interval was wide and was compatible with both reduction in miscarriage as well as increase, hence this review did not show progesterone to be effective in the treatment of threatened miscarriage.

One of the included studies (Palagiano 2004) has investigated the effect of progesterone on the relief of pain due to threatened miscarriage in a five-point scale 0-4 where 0 indicated no pain and 4 indicated extreme pain, and has shown significant reduction in the mean pain score with the use of progesterone from 2.6 ± 0.9 to 0.4 ± 0.7 (mean ± standard deviation) ($P < 0.01$), with no significant reduction in the pain score in the placebo group. These data could not be analyzed in this review as they were skewed.

To properly assess the effects of progestogens on threatened miscarriage, it is important to avoid the inclusion, in analyses, of women with similar clinical presentation but different underlying conditions such as those with viable and non-viable (missed miscarriage) pregnancies. We therefore specified the viability of the fetus, as confirmed by a reliable method, as an inclusion criterion for studies in this review.

The included studies did not include data about possible short- or long-term adverse effects of progesterone on the mother or the child, or both; consequently this review could not confirm or refute the concerns related to safety of the use of progesterone in the treatment of threatened miscarriage. Such concerns included a possible association between progestogen use and development of hypospadias in children conceived through in vitro fertilization (IVF) and whose mothers received progestogens in early pregnancy (Silver 1999). Such an increase in the incidence of hypospadias in this cohort may be accounted for by the general documented increase in the incidence of all congenital malformations in children conceived by IVF (Olson 2005); other population-based studies have not demonstrated this association (Dudas 2006; Katz 1985).

Threatened miscarriage is a common health problem, and miscarriage can cause serious morbidity among childbearing women. Any treatment which might prove to be effective is worth investigation.

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AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the routine use of progestogens for the treatment of threatened miscarriage. Information regarding the potential harm to the mother or child, or both, with the use of progestogens in the treatment of threatened miscarriage is lacking.

Implications for research

We strongly recommend investigation of the use of progestogens in this important and common health problem through multicentre methodologically-sound, randomized studies.

POTENTIAL CONFLICT OF INTEREST

None known.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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TABLES

Characteristics of included studies

Study	**Gerhard 1987**
Methods	Method of randomization unclear; allocation concealment unclear. The trial was double blinded. Power calculation was done with 95% confidence intervals. There was 12% dropout after randomization. Intention-to-treat analysis was not performed. Only 1 centre participated in this trial.
Participants	64 women randomized; 8 women excluded; 56 women analyzed. Only 35 participants included in this review as they had confirmation of fetal viability by ultrasound before commencement of treatment. There was no limitation of inclusion by previous obstetric history. Participants were accepted in the first trimester of pregnancy.
Interventions	25 mg; progesterone; twice daily vaginal suppositories versus placebo in the control group until the woman either miscarried or for 14 days after bleeding stops.
Outcomes	Miscarriage; birthweight; and preterm labour.
Notes	Only participants with confirmed viability were included in this review.
Allocation concealment	B – Unclear

Study	**Palagiano 2004**
Methods	Method of randomization generation is unclear; unit of randomization was threatened miscarriage; allocation concealment was adequate; both women and the treating team were blinded to the treatment; power

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	calculation was not done on miscarriage. Participant's dropout was reported but number was not specified. Intention-to-treat analysis was not done.
Participants	50 women with previous diagnosis of inadequate luteal phase, threatened miscarriage and confirmed fetal viability were included in the trial. Gestational age was 6-12 weeks.
Interventions	90 mg progesterone (Crinone 8%) vaginal suppositories once daily versus placebo in the control group for 5 days. The participants were followed for 60 days for the occurence of miscarriage and for 5 days for the other outcomes.
Outcomes	Pain relief miscarriage; frequency of uterine contractions; blood loss.
Notes	We will contact the trialists for data on the effect of progesterone on the pain related to threatened miscarriage so that, for the update, we can consider the possibility of transforming and analyzing the skewed data.
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	Reason for exclusion
Berle 1977	Combination therapy of progesterone and oestrogen was used in this study.
Berle 1980	Viability of the fetus was not confirmed before commencement of progesteron treatment.
Brenner 1962	The outcomes for this study were not applicable to this review. Treatment was not given to participants until 38 weeks of gestation. The outcome measured was time from onset of labour to delivery.
Check 1995	The intervention in this study is progesterone in combination with immunotherapy rather than progesterone alone.
Corrado 2002	This study does not investigate women with threatened miscarriage but women who have undergone amniocentesis.
Crowder 1950	In this study, viability was not confirmed by a reliable method. Progesterone was used with stilbestrol. More than 20% of participants were excluded from analysis after randomization.
El Zibdeh 2000	This study investigates women with recurrent miscarriage and not those with threatened miscarriage.
El Zibdeh 2002	This study investigates women with recurrent miscarriage and not those with threatened miscarriage.
El Zibdeh 2005	This study investigates women with recurrent miscarriage and not those with threatened miscarriage.
Fuchs 1966	Trial was terminated before data collection was completed. The study was addressing habitual abortion rather than threatened abortion.
G-Videtzky 1965	Viability of the fetus was not confirmed before commencement of progesteron treatment. No information is available to facilitate further statistical analysis.
Goldzieher 1964	This study investigates women with recurrent miscarriage and not those with threatened miscarriage.
Johnson 1975	This study investigates women at high risk of preterm labour and not those with threatened miscarriage. Progesterone was used for prevention of preterm labour.
Klopper 1965	This study investigates women with recurrent miscarriage and not those with threatened miscarriage.
Le Vine 1964	This study investigates women with recurrent miscarriage and those not those with threatened miscarriage.
Luz 1988	Progesterone was used in combination with oestrogen in the treatment of threatened miscarriage.
Moller 1965	Viability of pregnancy was not reliably confirmed by ultrasound scan.
Nyboe 2002	This study investigates women who underwent assisted reproduction and not those with threatened miscarriage.
Omar 2005	More than 20% of the randomized women were lost to follow up and excluded from the analysis.
Prietl 1992	This study does not investigates women with threatened miscarriage. Progesterone and oestrogen were both given in IVF pregnancy to assess the effect on the development and the outcome of pregnancy.
Reijnders 1988	This study does not investigates women with threatened miscarriage.

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Characteristics of excluded studies (*Continued*)

Shearman 1963	This study investigates women with recurrent miscarriage and not those with threatened miscarriage.
Smitz 1992	This study does not investigate women with threatened miscarriage but women with assisted reproduction. Intramuscular progesterone was compared to vaginal progesterone rather than placebo or no treatment.
Sondergaard 1985	This study investigates women with preterm labour rather than threatened miscarriage.
Souka 1980	Viability of pregnancy was not confirmed by a reliable method such as ultrasound scan.
Swyer 1953	This study investigates women with recurrent miscarriage and not those with threatened miscarriage.
Tognoni 1980	The viability of the fetus was not confirmed by a reliable method such as ultrasound scan.
Turner 1966	The outcome of this study is irrelevant to this review. Progesterone was given at 30 weeks of pregnancy.

IVF: in vitro fertilization

ANALYSES

Comparison 01. Progesterone versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Miscarriage	2	84	Relative Risk (Fixed) 95% CI	0.47 [0.17, 1.30]
02 Pain score	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Threatened [*drug therapy]; Progestins [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Progestogen for treating threatened miscarriage
Authors	Wahabi HA, Abed Althagafi NF, Elawad M
Contribution of author(s)	Dr Hayfaa Wahabi participated in the selection of eligible studies and in the appraisal of the selected studies. She wrote both the initial and final version of the review. Dr Mamoun Elawad participated in the selection of the eligible studies, the appraisal of the selected studies, and commented on the initial and final versions of the review. Dr Nuha Abed Althagafi participated in the selection of the eligible studies and the appraisal of the selected studies.
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Date new studies sought but none found	Information not supplied by author

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Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	30 December 2006
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Progesterone versus placebo, Outcome 01 Miscarriage

Review: Progestogen for treating threatened miscarriage

Comparison: 01 Progesterone versus placebo

Outcome: 01 Miscarriage

Study	Progesterone n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gerhard 1987	0/17	1/17		15.8	0.33 [0.01, 7.65]
Palagiano 2004	4/25	8/25		84.2	0.50 [0.17, 1.45]
Total (95% CI)	**42**	**42**		**100.0**	**0.47 [0.17, 1.30]**

Total events: 4 (Progesterone), 9 (Placebo)

Test for heterogeneity chi-square=0.06 df=1 p=0.81 I^2 =0.0%

Test for overall effect z=1.45 p=0.1

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Analysis 01.02. Comparison 01 Progesterone versus placebo, Outcome 02 Pain score

Review: Progestogen for treating threatened miscarriage

Comparison: 01 Progesterone versus placebo

Outcome: 02 Pain score

Study	Progesterone N Mean(SD)	Placebo N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	**0**	**0**		**0.0**	**Not estimable**
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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